REACTIVITY STUDIES OF NOVEL FLUORINATED BUILDING BLOCKS: 1,1-BIS(DIMETHYLAMINO)-2,2,2-TRIFLUOROETHANE AND 1,1-BIS(DIMETHYLAMINO)-2,2-DIFLUOROETHENE

By

YUELIAN XU

A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL
OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

UNIVERSITY OF FLORIDA

1999

To my wife, Hua Lou, and my daughter, Qingqing,
with love

ACKNOWLEDGMENTS

I am deeply indebted to my supervisor, Professor William R. Dolbier, Jr., for his invaluable guidance, encouragement, and trust over the years. It has been a rewarding experience and a pleasure to work with him.

I would also like to take this opportunity to express my sincere gratitude to Drs. Merle A. Battiste, Kirk S. Schanze, David H. Powell, Hai Ping Cheng, Denis Wright and Gus Palenik for their help, suggestions and time they have spent as my supervisory committee members.

I would like to give my special thanks to Dr. Xiaoxin Rong, Lian Luo for his valuable help and cooperation during my early stay at Gainesville. My thanks also go to all Dolbier group members and my friends outside who are too many to mention individually, for their support and friendship.

I am deeply indebted to my parents and my parents in-law for their support and encouragement, without which I could not have become a doctor.

Last but not the least, I am extremely grateful to my wife, Hua Lou, for her constant understanding, support and critical mind, and for everything she has done for me.

TABLE OF CONTENTS

ACKNOWLEDGMENTS iii

ABSTRACT vi

CHAPTERS

1 AN OVERVIEW: SYNTHESIS UTILITIES OF TRIFLUOROACETALDEHYDE, DIFLUORO ENOLATES, AND THEIR EQUIVALENTS 1

1.1 Introduction 1
1.2 CF_3-building Blocks as Intermediates 3
1.3 Difluoro Enolates and Enolate Equivalents 17

2 TRIFLUOROMETHYLATED AMINALS: SYNTHESIS AND UTILITY AS TRIFLUOROMETHYLATED BUILDING BLOCKS 32

2.1 Introduction 32
2.2 Results and Discussion 33
2.3 Experimental 42

3 SYNTHESIS OF TRIFLUOROMETHYLATED AMINES USING 1,1-BIS(DIALKYLAMINO)-2,2,2-TRIFLUOROETHANES 51

3.1 Introduction 51
3.2 Results and Discussion 52
3.3 Experimental 59

4 DIFLUORO KETENE AMINAL: SYNTHESIS AND REACTIVITY 69

4.1 Introduction 69
4.2 Results and Discussion 71
4.3 Experimental 77

5 CYCLOADDITION REACTIONS OF 1,1-BIS(DIMETHYLAMINO)-2,2-DIFLUOROETHENE 87

5.1 Diverse Cycloaddition Chemistry Leading to Overall Michael Addition in the Reaction of 1,1-Bis(dimethylamino)-2,2-difluoroethane with α,β-Unsaturated Aldehydes, Ketones, Esters, and Nitriles 87
5.2 Synthesis of Monofluoro-Aminopyridine 92
5.3 1,3-Dipolar Cycloaddition 96
5.4 Synthesis of Novel Fluorinated Derivatives of 1,3-Dimethylbarbituric Acid 98
5.5 Experimental 104

6 SYNTHESIS AND MECHANISTIC ASPECTS OF THE REACTION OF 1,1-BIS(DIMETHYLAMINO)-2,2-DIFLUOROETHENE WITH ETHYL PROPIOLATE 125

6.1 Introduction 125
6.2 Results and Discussion 126
6.3 Experimental 135

REFERENCES 147

BIOGRAPHICAL SKETCH 159

Abstract of Dissertation Presented to the Graduate School
of the University of Floridain Partial Fullfillment of the
Requirements for the Degree of Doctor of Philosophy

REACTIVITY STUDIES OF NOVEL FLUORINATED BUILDING BLOCKS:
1,1-BIS(DIMETHYLAMINO)-2,2,2-TRIFLUOROETHANE
AND 1,1-BIS(DIMETHYLAMINO)-2,2-DIFLUOROETHENE

By

Yuelian Xu

December 1999

Chairman: William R. Dolbier, Jr.
Major Department: Chemistry

1,1-Bis(dimethylamino)-2,2,2-trifluoroethane (**73**) has been successfully prepared from 1,1-dichloro-2,2,2-trifluoroethane and dimethylamine in the presence of copper. It has been used as a synthetic building block for the synthesis of various trifluoromethylated compounds and as a precursor to the novel fluorinated building block 1,1-bis(dimethylamino)-2,2-difluoroethene (**103**).

1,1-Bis(dimethylamino)-2,2,2-trifluoroethane undergoes direct acid catalyzed condensation reactions with ketones to form β-keto trifluoromethylcarbinols. Silyl enol ethers undergo a ZnI_2-catalyzed condensation with **73** to form α,β-unsaturated products of the general structure, $CF_3CH{=}CRCOR$. It reacts with cyanotrimethysilane and allyltrimethylsilane in the presence of ZnI_2 to afford α-trifluoromethylated compounds in high yields. Trifluoromethylated propargylamines are formed upon reacting with acetylene under catalysis by CuI or ZnI_2.

Treatment of **73a** with 1.1 equivalents of butyllithium leads to the formation of 1,1-bis(dimethylamino)-2,2-difluoroethene (**103**). The reactivity of **103** shows both nucleophilic and electrophilic behavior. It undergoes quantitative reaction with water, bromine, or iodine to give the respective N,N-dimethyldifluoroacetamide, -bromodifluoroacetamide, and -iododifluoroacetamide. It condenses with various substituted benzaldehydes to give good yields of the respective N,N-dimethyl-2,2-difluoro-3-hydroxy-3-arylpropionamides. **103** was found to undergo a facile addition-elimination process upon addition of 1 equivalent of alkyllithium at room temperature, and upon hydrolytic workup one could obtain reasonable yields of α-fluoroacetamides. Acylation of **103** with various acid chlorides gave products of the general structure, $RCOCF_2CONMe_2$, upon workup. It was also found that **103** could condense with various carbon acids, such as malononitrile, nitromethane, ethyl cyanoacetate to form difluoromethylated enamines.

Compound **103** undergoes clean [2+4] cycloaddition with α,β-unsaturated aldehydes and ketones and clean [2+2] cycloadditions with α,β-unsaturated esters and nitriles. Both types of adducts proved to be readily converted, by mild hydrolysis, to the overall Michael addition products. 1,3-Dipolar cycloaddition of **103** with N-phenylnitrones forms the respective difluoropropioamides. The synthetic utility of **103** was extended to the preparation of a number of potentially biologically interesting difluoro barbituric acid derivatives via initial hetero-Diels-Alder reaction of **103** with p-substituted-5-benzylidene-1,3-dimethylbarbituric acids. These cycloadducts upon hydrolysis provided the formal Michael addition product amides, which were readily

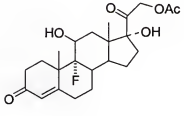
converted to the respective carboxylic acids. The acids were dehydratively cyclized to form novel bicyclic lactones.

1,1-bis(dimethylamino)-2,2-difluoroethene (**103**) undergoes a [2+2] cycloaddition with ethyl propiolate at -25°C [$\Delta H^{\neq}$ = 4.2 (+0.4) kcal/mol and $\Delta S^{\neq}$ = -56.7 (+0.9) cal/molK], and the cyclobutene product undergoes electrocyclic ring opening at +15°C [$\Delta H^{\neq}$ = 18.5 (+0.6) kcal/mol and $\Delta S^{\neq}$ = -9.7 (+1.0) cal/molK]. The resulting diene undergoes Diels Alder reactions with electron deficient dienophiles to give aromatic products.

CHAPTER 1
AN OVERVIEW: SYNTHETIC UTILITIES OF TRIFLUOROACETALDEHYDE, DIFLUORO ENOLATES, AND THEIR EQUIVALENTS

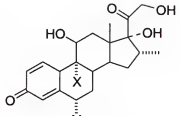
1.1 Introduction

Selective introduction of fluorine into organic molecules often imparts dramatic alternations in structure and reactivity. It was the pioneering work of Fried in the preparation of 9α-fluorohydrocortisone acetate[1] (**1**) that led to the first significant report of the successful application of selective fluorination to modify biological activity. 9α-fluorohydrocortisone acetate could be used as gluco corticoid and its activity was 9-10 times higher than non-fluorinated derivatives. Since then, medicinal chemists and biochemists routinely introduced fluorine as a substituent to modify activity. A number of medicinal agents have been developed in which fluorine substitution has been a key to their biological activity,[2] such as anticancer agents 5-fluorouracil[3] (**2**), and the anti-inflammatory glucocorticoids[4] parmethasone (**3**) (X=H, Y=F), and dexamethasone (**4**) (X=F, Y=H).



1

2



3,4

The enhancements of biological activity using selectively fluorinated biologically important compounds stem from four major characteristics inherent to the fluorine atom:

1.Fluorine and hydrogen are comparable in size (van der Waals radius 1.35 Å versus 1.20 Å). The substitution of fluorine for hydrogen results in minimal change of the steric requirements of the molecule. This allows fluorinated analogues to follow the metabolic pathway of the parent hydrogen compounds leading finally to their incorporation into the organism.[5]

2.Fluorine is the most electronegative element (H 2.1; C 2.5; Cl 3.0; O 3.5; F 4.0 in Pauling's scale) and it alters the electron density, basicity, and acidity of neighboring groups. The chemical and enzymatic reactivity of surrounding functionalities is affected and the conformation of the whole molecule may be changed due to dipole interactions. As a consequence of available electron density, fluorine can function as a hydrogen bond acceptor.[6]

3.The carbon-fluorine bond is at least 14 kcal/mole stronger than the carbon-hydrogen bond, and as a consequence, the introduction of fluorine makes the substrate relatively resistant to metabolic transformations. This property has been exploited in attempts to prolong the action of a drug by blocking the sites involved in oxidative degradation.[7]

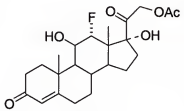
4.Fluorinated compounds are highly lipophilic. This property may contribute to the absorption, transport, and delivery of an agent to its biological target, which is a preliminary process to its activity.

Concomitant with an increased understanding of the behavior of organofluorine compounds, considerable progress has also been made in the development of new

synthetic methodologies.[8] In our laboratory, we developed a method for the synthesis of novel trifluoromethylated aminal system and its derivatives, difluoroketene aminal,[9] which are used as CF_3-, CF_2-building blocks in construction a variety of trifluoromethylated and *gem*-difluorinated organic compounds. It is the purpose of this overview to review some of the related synthetic methodologies.

1.2 CF_3- Building Blocks as Intermediates

The effect of the biological activity by the introduction of fluorine is closely related to the position of fluorine atom in the organic compounds. For example, where the activity of compound (**1**) as a glucocorticoid is higher than the analogous non-fluorinated derivative, another fluorinated derivative (**5**) showed no activity.



5

The only difference of compound (**1**) and (**5**) is in the position of substitution. This indicates that the fluorinated biological compound requires highly selective introduction of the fluorine substitute. Now, extensive research has already been carried out on incorporation of fluorine into molecules. Generally, two approaches are used for the selective introduction of fluorine atoms into organic molecules. First, using fluorinating reagents directly or indirectly introduce fluorine substituents. Examples of such reagents are elemental fluorine,[10] xenon difluoride,[11] hydrogen fluoride,[12] SF_4[13] etc.

However, the explosive, hazardous nature or expense of these reagents, the low yield or poor selectivity of the reactions, or the extremely severe reaction conditions has strictly limited their practical application. Finding milder and higher selective fluorinating reagents is still the goal of fluorine chemists. Presently, several mild fluorinating agents have been developed in the synthesis of fluorinated organic compounds, including DAST[14] and various N-F compounds.[15]

Secondly, using fluorinated building blocks construct fluorine-containing target molecules from fluorine-containing starting materials by carbon-carbon bond formation to the fluorinated fragment.[16] Easy to handle and relatively available fluorinated building blocks make this approach quite attractive. The building block approach doesn't involve the breakage and formation of C-F bond, and it shows quite high selectivity in the synthesis of certain compounds. Also, through a building block, we can synthesize a variety of fluorinated compounds. Figure 1-1 depicts one example,[17] compound (**6**) which reacts with a variety of reagents to give 5-membered heterocyclic compounds incorporating the CF_3-group.

Building blocks containing the CF_3 function represent a great number of specific types.[18] (1) Compounds containing CF_3 group themselves represent an important class of fluorinated organic compounds. (2) CF_3 group has the strongest lipophilicity in all of the functional group. (3) A number of compounds containing CF_3 group show biological activities, the following compounds (**7-9**) are some of the examples (Figure 1-2).[19,20] (4) Trifluoromethylated aromatics can be prepared by direct fluorination of other functional groups,[13,14,21] such as COOH to CF_3, CX_3 to CF_3 by fluorine and halogen exchange. However, trifluoromethylated aliphatic compounds are difficult to prepare via

this method. (5) Under certain conditions, CF_3 building blocks can be transferred to aliphatic systems by suitable chemistry.[18] Therefore, the study of the CF_3 building block remains great interest. Table 1-1 lists some typical CF_3 building blocks that are in the literature.

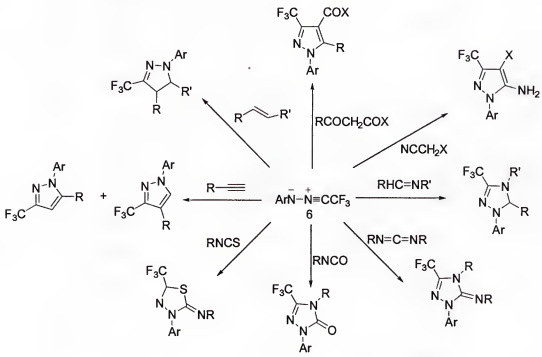
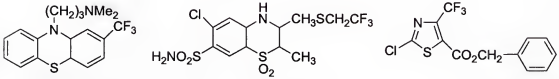


Figure 1-1. Typical example of the synthesis of fluorinated compounds using a fluorinated building block.



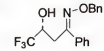
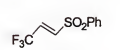
7 Triflupromazine (Tranquilizer)

8 Polythiazide (Hypertension)

9 Fluorozole (Herbicide)

Figure 1-2. Examples of modern fluorine-containing biological active compounds.

Table 1-1. CF_3 Building blocks containing CF_3 group

[22]	[22]	X = Cl, I [23,24]	[25]	[26]	 [27]
[28]	[29]	[30]	[31]	[32]	X = H, Br [33,34]
[35]	[36]	 [37]	[38a]	[38b]	

1.2.1 Trifluoroacetaldehyde and Its Equivalents

Among the many building blocks approaches to trifluoromethylated organic compounds, trifluoroacetaldehyde (**10**), along with its derivatives, comprise some of the most useful compounds for the synthesis of trifluoromethylated compounds via use of a number of reagents. Reactions of trifluoroacetaldehyde with a variety of nucleophiles, such as organometallic reagents (Grignard,[39] Reformatsky,[40] Wittig,[41] lithium reagents[42]), metal enolates,[43] ketene silyl acetals,[44] and aromatic compounds,[45] olefins and dienes,[46] generate the respective carbinols. Condensation reactions of trifluoroacetaldehyde with active methylene compounds form useful trifluoromethylated compounds, which are used further as CF_3 building blocks. Figure 1-3 represents some of the transformations of trifluoroacetaldehyde.

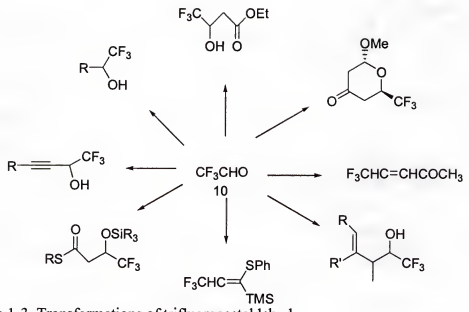


Figure 1-3. Transformations of trifluoroacetaldehyde.

However, trifluoroacetaldehyde is gaseous (bp $-18^{\circ}C$) and very unstable, and usually is generated *in situ* from its hydrate or alkyl acetal. The methods for the actual generation of trifluoroacetaldehyde require high temperatures and an excess amount of concentrated H_2SO_4.[47] Also, the chemical or electrochemical oxidative transformation of trifluoroethanol to trifluoroacetaldehyde has been unsuccessful. Trifluoroacetaldehyde is therefore generally produced by the reduction of trifluoroacetic acid ester or acid chloride using an excess of lithium aluminum hydride (LAH).[2a] Such limitations encouraged people to find alternative ways to form trifluoroacetaldehyde.

Direct usage of commercially available trifluoroacetaldehyde hydrate or alkyl hemiacetals to form trifluoromethylated organic compounds should be most efficient and convenient. Also, several reagents have been developed to use as trifluoroacetaldehyde equivalents.

Condensation of trifluoroacetaldehyde hydrate or alkyl hemiacetals with amino compounds to form Schiff bases has been studied extensively.[48] Usually, the Schiff bases were continually used to construct useful trifluoromethylated building blocks.[48] Reaction of trifluoroacetaldehyde ethyl hemiacetals with primary amines form trifluoromethylated imines, which are used for the synthesis trifluoromethyl-azetidinones.[49] Trifluoromethylated imidazolidines[50] and oxazolidines[51] can be easily prepared by treatment of aldehyde hydrate with diamines or α-amino alcohol. The asymmetric synthesis of substitute trifluoroethylamines has been achieved through a stetreospecific reduction of fluoral derived oxazolidines.[52]

Most useful application of the trifluoroacetaldehyde ethyl hemiacetal (TFAE) is to form α-trifluoromethylated alcohols. Several methods have been developed in this area.

Thermal condensation of indoles,[53] imidazoles,[54] and their derivatives[54] with trifluoroacetaldehyde ethyl hemiacetal (**11**) gave the corresponding (1'-hydroxy-2',2',2'-trifluoroethyl)indoles and (1'-hydroxy-2',2',2'-trifluoroethyl)imidazoles (Figure 1-4). Benzyl 3,5-dimethyl-2-pyrrolecarboxylate was converted to 4-(2,2,2-trifluoro-1-hydroxyethyl) derivatives on treatment with TFAE in the presence of zinc chloride. Friedel-Crafts type alkylation[55] using trifluoroacetaldehyde ethyl hemiacetal yields 1-phenyl-2,2,2-trifluoroethanol. The heteroatom-stabilized α-CF_3 cation is a presumed intermediate[55] in the reaction.

11 70%

Figure 1-4. Thermal condensation of indole with TFAE.

Trifluoroacetaldehyde ethyl hemiacetal reacted with nucleophilic organosilanes such as cyanotrimethylsilane, allytrimethylsilane, or enol trimethylsilyl ethers in the presence of Lewis acid to afford a series of α-trifluoromethylated alcohols in high yield[56] (Figure 1-5).

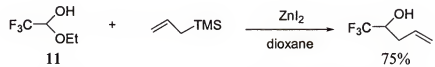


Figure 1-5. Synthesis of 1-trifluoromethylated homoallylic alcohol.

Indium-mediated allylation reaction and tin-mediated indium trichloride-promoted allylation reaction of trifluoroacetaldehyde hydrate and its ethyl hemiacetal has been developed by Loh et al[57] (Figure 1-6).

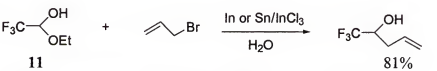
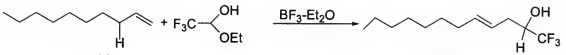


Figure 1-6. Indium-mediated allylation of TFAE.

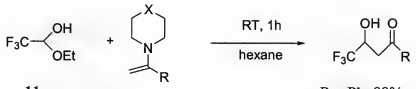
Ene-type reactions[58] of trifluoroacetaldehyde hemiacetal with ene compounds in the presence of Lewis acid form α-trifluoromethylated homoallyl alcohols, the same products as those from the ene reaction of trifluoroacetaldehyde,[46] in moderate to good yields (Figure 1-7). Boron trifluoride etherate was found to be the most effective catalyst in this reaction.



11 75%

Figure 1-7. Ene-type reaction of TFAE with ene compounds in the presence of a Lewis acid.

Normally, trifluoroacetaldehyde was generated at high temperatures and using an excess amount of contrentrated H_2SO_4. Shibata et al.[59] discovered that trifluoroacetaldehyde ethyl hemiacetal readily reacts with various enamines in hexane at room temperature for 1 hour to give the corresponding β-hydroxy-β-trifluoromethyl ketones in good yields (Figure 1-8). The trifluoroacetaldehyde was proposed as intermediate, which was generated under the reaction conditions.



11 R = Ph; 88%

Figure 1-8. Reaction of TFAE with enamine.

Fuchigami's group reported that the trifluoromethyl group promoted anodic methoxylation and acetoxylation of aryl 2,2,2-trifluoroethyl sulfides and N-(trifluoroethyl)amines to form trifluoroacetaldehyde N,O-[60] and O,S-acetals.[61] These trifluoroacetaldehyde N,O- and O,S-acetals have been demonstrated to be good trifluoroacetaldehyde equivalents. These trifluoroacetaldehyde acetals were used to form carbon-carbon bonds under Lewis acid catalysis, which generated a carbocation

intermediate stabilized by the neighboring group. The related chemistry of such trifluoromethyl carbocations will be discussed in the following section.

1.2.2 α-Trifluoromethyl Cations in Synthetic Applications

Generally, generation of carbocations bearing an α-trifluoromethyl group is difficult due to the strong electron withdrawing effect of the CF_3 group.[62] Nonetheless numerous studies have now firmly established such cations as viable and fascinating intermediates. Also, a number of syntheses have been carried out which involve α-CF_3-substituted cationic intermediates. Among these are those methods used to introduce functionality adjacent to the CF_3 group.

Viehe has prepared a variety of CF_3-substituted derivatives starting from (1,1-dichloro-2,2,2-trifluoroethyl)dimethylamine[63](**12**) (Figure 1-9). This α-chloro amine reacted with dimethylamine to give the perchlorate derivative as an isolable salt after ion exchange. Reaction with Me_2NCN led to the highly delocalized salt, while reaction with 1,3-propanediol and phenylenediamine gave the acetal and the heterocyclic product, respectively. The CF_3-substituted iminium cation (**13**) is proposed as an intermediate.

Also, the same author prepared α-trifluoromethyl iminium trifluoacetates (**15**) from N-oxides of trifluoroethylamines (**14**)[64] (Figure 1-10). These iminium salts of fluoral reacted with ketone to form β-trifluoromethyl vinyl ketones. Treatment of thioamide (**16**) with methyl triflate give trifluoromethyl thioamidium salt (**17**) and deprotonation of salt (**17**) generates trifluoromethyl azomethine ylides[65] (Figure 1-10), which was trapped by dipolarphiles.

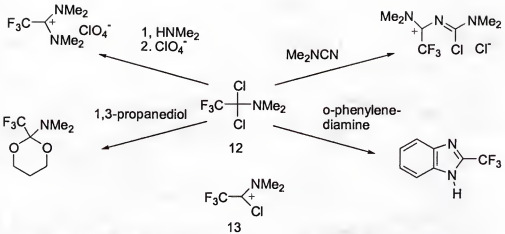


Figure 1-9. Reactions of (1,1-dichloro-2,2,2-trifluoroethyl)dimethylamine.

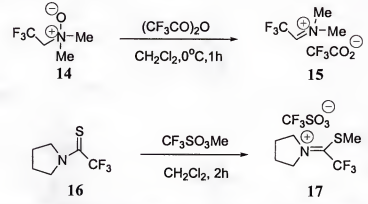


Figure 1-10. Generation of trifluoromethyl iminium and thioamidium salts.

As mentioned before, Fuchigami has prepared the methyl ether (**20**) and acetate (**21**) by anodic oxidation of compound (**18**).[61a,b] These oxidations presumably involve the α-CF_3 cation (**19**), which is trapped by a nucleophile under the oxidation conditions (Figure 1-11). Alternatively, Pummerer rearrangement of sulfoxide (**22**) gave only a 42% yield of the acetate (**21**). Lewis acid promoted nucleophilic substitution of **20** with arenes has been successfully achieved to give compound **23**[61c] (Figure 1-11).

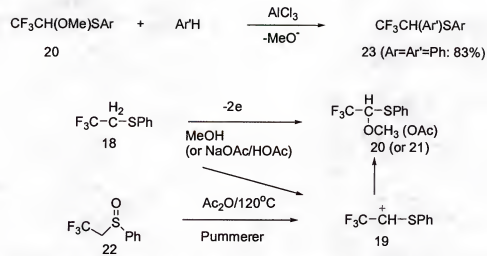


Figure 1-11. Formations and reactions of trifluoroacetaldehyde O,S-acetals.

Anodic oxidation of the amines (**24**) in an alkaline methanol solution gave the α-methoxylated product (**25**).[60] The radical cation (**26**) and the α-CF_3-substituted cation (**27**) (an iminium cation) are suggested as intermediates. Treatment of the methyl ether (**25**) with $TiCl_4$ regenerated the cation (**27**), which could be trapped by carbon nucleophiles. Reaction with trimethylsilyl cyanide gave the nitrile (**28**), while reacting with the silyl enol ether of cyclohexanone provideed the heterocyclic compound (**29**) (43%) along with the amino ketone (**30**) (27%) (Figure 1-12).

The cationic polar cycloaddition of α-methoxylated amine (**31**) with nucleophilic unsaturated compounds such as styrenes or phenylacetylene in the presence of $TiCl_4$ gave trifluoromethylated tetra (51-86%) (**32**), and dihydroquinoline derivatives (70%) (**33**) (Figure 1-13).

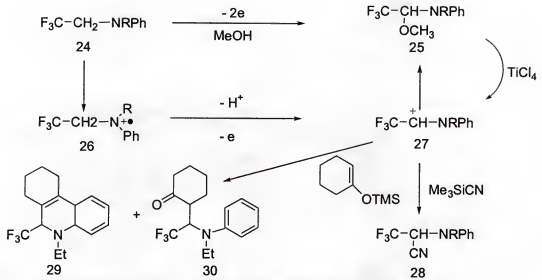


Figure 1-12. Formations and reactions of trifluoroaldehyde O,N-acetals.

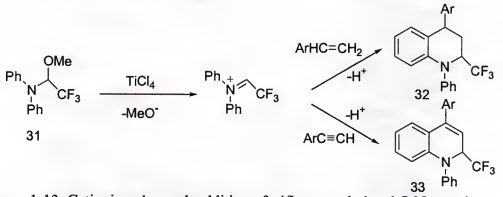


Figure 1-13. Cationic polar cycloaddition of trifluoromethylated O,N-acetal.

Umiyama has prepared α-chloro sulfide (**34**). Cation 19, generated under Lewis acid conditions, can be trapped by aromatic substrates[66] (Figure 1-14). The rate of consumption of **34** by arene proceeded in the order anthracene> toluene> benzene> chlorobenzene. This suggests that the arene may participate intermolecularly in the rate-determining step. The reaction of optically active **34** with naphthalene gave a racemic product, as well as racemized **34**, when the reaction was interrupted after a short time.

Allylation of **19** was achieved by treatment with allyltrimethylsilane, and reaction with several nitriles formed amides.

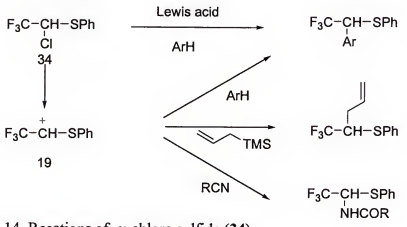


Figure 1-14. Reactions of α-chloro sulfide (**34**).

Intramolecular arylation of sulfur-stabilized α-CF_3 cation (**36**) (derived from **35** under Lewis acid conditions) was obtained[66] (Figure 1-15). Only intermolecular reactions were observed in the system **37** with one less methylene group.

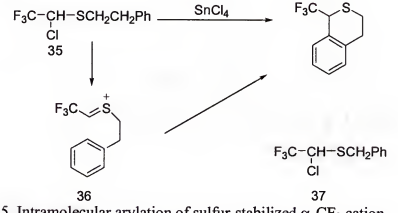


Figure 1-15. Intramolecular arylation of sulfur-stabilized α-CF_3 cation.

The secondary triflates **38** lead to the CF_3-substituted tetralines **39** under trifluoroacetolysis conditions[67] (Figure 1-16). These cyclizations are proposed to occur via processes involving aryl ring participation since the discrete secondary α-CF_3 cation is presumably quite unstable. 4-Chloro- or 4-methoxy-substituted analogues of **38** did not cyclize under these conditions.

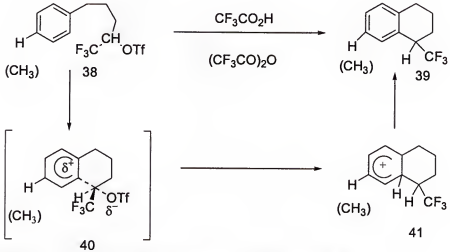


Figure 1-16. Cyclization of trifluoromethylated triflate **38**.

The alcohols **42** also give CF_3-substituted tetralins **43** when heated in CF_3COOH containing 0.02 M sulfuric acid[67] (Figure 1-17). Rates were independent of the substituent R, but quite dependent on the substituent on the Ar group. This reflects the high degree of cationic character in the intermediate which leads to cyclization.

Condensation of the hemiacetal derivative of trifluoroacetaldehyde (**11**) with aromatic compounds under Lewis acid or protic acid conditions gave varying amounts of products **46–49**[45] (Figure 1-18). The oxygen atom stabilized α-CF_3 cation **50** is a presumed intermediate.

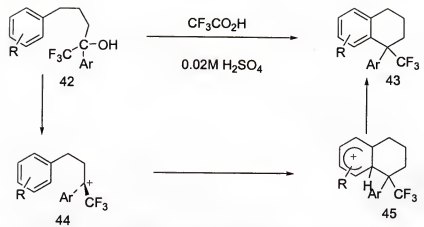


Figure 1-17.Cyclization of trifluoromethylated alcohols **42**.

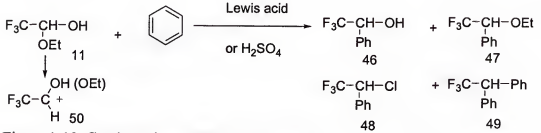


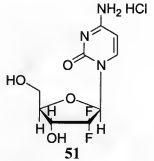
Figure 1-18. Condensation of TFAE with benzene.

In conclusion, trifluoroacetaldehyde and its synthetic equivalents have been versatile building blocks for the synthesis of trifluoromethylated organic compounds. The generation of carbocations bearing an α-trifluoromethyl group and the carbon-carbon bond formation reactions of trifluoroacetaldehyde and its equivalents are remarkable from both mechanistic and synthetic aspects.

1.3 Difluoro Enolates and Enolate Equivalents

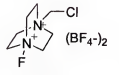
Difluoromethylene compounds have attracted much attention due to their unique physical, chemical and biological properties. Particularly, the *gem*-difluoromethylene

group has a unique electronic nature to act as an isoelectronic and isosteric replacement for oxygen, which contributes to the formation of stable hydrate and hemiketals,[68] purporting to mimic the tetrahedral transition states. Recent works have revealed a wide range of biologically interesting difluoromethylene compounds[69] such as anticancer agent 2-deoxy-2,2-difluorocytidine (**51**) (gemcitabine),[70a] HIV-1 protease inhibitors,[70b] and phosphotyrosine (pTyr) mimetics.[70c]



51

Gemcitabine



52

Selectfluor (F-TEDA-BF_4)

A wide variety of methods have been developed for the synthesis of functionalized *gem*-difluoromethylene compounds,[71] and in principle, they can be divided into two classes of reaction. The first type is the transformation of a ketonic carbonyl group or its equivalents using nucleophilic or electrophilic fluorinating reagents such as diethylaminosulfur trifluoride (DAST),[14] NBS-HF-amine complexes,[72a] N-fluoro compounds (**52**) (Selectfluor),[72b] and the reaction of difluorocarbenes[72c] and so on. However, these approaches are limited by the requirement to deploy a carbonyl group at the strategic position of suitably protected precursors, also by the hazardous and reactive nature of most fluorinating reagents. The second type is CF_2-synthon approach, which is more attractive method to incorporate *gem*-difluoromethylene group into organic

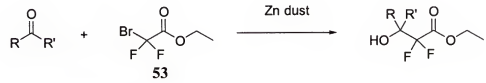
compounds using various CF_2 building blocks. Several account papers reviewed this related topics.[71] Especially in the CF_2-synthetic intermediates, fluorinated enolates[71] (difluoro enol ether and difluoroketene silyl acetals) play an important role in the synthesis of *gem*-difluoromethylene compounds due to their ambiphilic character, which allows them to exhibit either nucleophilic or electrophilic character in their reactions. Their synthetic utilization has been demonstrated in fluorinated sugars and amino acid syntheses.[2a]

Reformatsky-type reactions of halodifluoroacetates have been widely used to synthesize the difluoroketene silyl acetals. Also, selective defluorinations from a trifluoromethyl group such as base-catalyzed dehydrofluorination of a 2,2,2-trifluoroethyl group, chemical and electrochemical reductive defluorination of trifluoromethyl ketones and trifluoroacetic acid derivatives, and Brook-type rearrangement of trifluoroacetylsilanes have been systematically studied. We developed difluoroketene aminal systems by the dehydrofluorination of trifluoromethylated aminals. In this chapter, an overview of pertinent background information for the formation and the reactivity of fluorinated enolates and their synthetic equivalents will be discussed.

1.3.1 The Reformatsky and Related Reactions

The Reformatsky reaction of halodifluoroacetates and halodifluoroketones is by far the most common of all the CF_2-synthon approaches. Its products are versatile intermediates which have found significant use in the synthesis of peptidase inhibitors designed around α,α-difluoroketones.[2c]

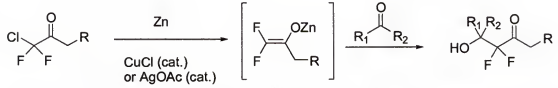
Fried described the preparation of 2,2-difluoro-3-hydroxy esters by the Reformasky reaction of ethyl bromodifluoroacetate (**53**) with aldehydes and ketones (Figure 1-19) in 1984.[74]



53

Figure 1-19. Reformatsky reaction of bromodifluoroacetate.

At same time, Ishihara reported that chlorodifluoromethyl ketones (**54**) reacted with carbonyl compounds to form 2,2-difluoro-3-hydroxy ketones in the presence of zinc and catalytic amount of titanium tetrachloride[75] (Figure 1-20). This procedure was improved by using copper chloride as a catalyst for the reaction with aldehydes and silver acetate with ketones.[76,77] The intermediate zinc enolate (**55**) has been observed by ^{19}F NMR.



54 **55**

Figure 1-20. Formation and reaction of zinc difluoro enolate.

Since Fried's initial report, several modified methods for this reaction using either chloro-,[78] bromo-, or iododifluoroacetate with various additives have been published mainly from the view of the activation of zinc. Addition of a catalytic amount of $CeCl_3$[79]

or Et_2AlCl with a catalytic amount of AgOAc[80] facilitated the use of milder conditions. Ultrasonic activation of a preformed organic zinc reagent allowed the Reformatsky reaction to be carried out with aldehydes and ketones bearing a nitro group.[81] An electrochemical nickel catalyzed reaction with methyl chlorodifluoroacetate and a sacrificial zinc anode,[81] and electrochemical reductive couplings of methyl chlorodifluoroacetate with aldehydes using a lead cathode has been reported.[82] Iyoda [83] reported that samarium diiodide (SmI_2) as an alternative reagent to Zn for the reactions of XCF_2COOEt (X=Cl and Br) with aldehydes and ketones giving 2,2-difluoro-3-hydroxy esters effectively and practically at room temperature. Zinc cuprate of ethyl bromodifluoroacetae underwent a substitution reaction with allylic halides in S_N2 manner.[84]

The zinc enolates formed under Reformatsky conditions could be trapped as their trimethylsilyl derivatives (Figure 1-21). The silyl enolates generated from halodifluoroketones[85] could be isolated but those ketene silyl acetals generated from halodifluoroesters[86] were unstable and are usually reacted *in situ*, with the zinc dihalide acting as a Lewis acid. Both types of enolates condensed with aldehydes and ketones. Ketene silyl acetal also underwent Michael additions[87] and nucleophilic substitutions[88] as depicted in Figure 1-21.

Enantioelective reactions of difluoro enolates have been attempted. Braun et al disclosed the first enantioselective Reformatsky reaction of a bromodifluoroacetate. Benzaldehyde reacted with with an excess of the Reformatsky reagent, prepared from zinc and methyl bromodifluoroacetate (3 equiv.), in the presence of the chiral β-amino

alcohol (**56**) to provide the corresponding α,α-difluoro-β-hydroxy ester in 61% yield and with 84% ee. (Figure 1-22).[89]

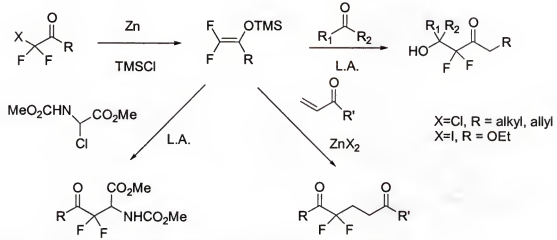


Figure 1-21. Formations and reactions of difluoro sily enolates.

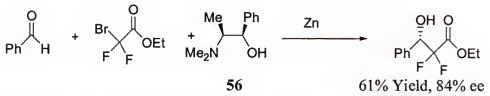
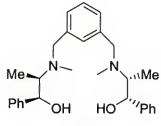


Figure 1-22. Enantioselective Reformatsky reaction of bromodifluoroacetate.

Anders and coworkers also reported the asymmetric synthesis of optically active α,α-difluoro-β-hydroxy ester using chiral aminoalcohol ligands (**57**). However, both chemical and optical yields were insufficient.[90]

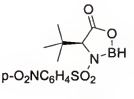
In 1997, Iseki and coworkers reported the first example of the asymmetric Mukaiyama aldol reaction of difluoroketene silyl acetals catalyzed by chiral Lewis acid.[91] The pure form of the difluoroketene ethyl silyl acetal (**60**) was isolated (Figure 1-23) and the aldol reaction was performed using chiral Lewis acid catalysts. As shown in

Figure 1-24, two chiral boron complexes, Masamune's (**58**) and Kiyoka's catalysts (**59**), gave high ee.

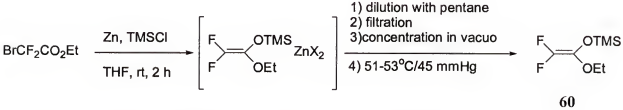


57

58

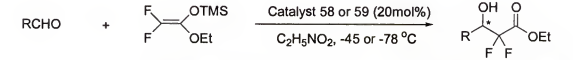


59



60

Figure 1-23. Isolation of difluoroketene ethyl trimethylsilyl acetal.



60 (1.2 equiv.) 90-99% Yield, 92-98% ee

Figure 1-24. Asymmetric aldol reaction catalyzed by chiral Lewis acids.

1.3.2 Other Difluorinated Enolates

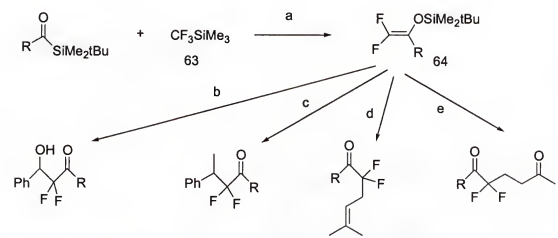
Other approaches to the formation of difluoroenolates have appeared in the literature. Trifluoroacetyltriphenylsilane (**61**) reacted with an organometallic reagent to form difluoroenoxysilane (**62**) by the Brook rearrangement.[92] The silylenol ethers (**62**)

reacted with aldehydes and ketones with good diasteroselectivity in the presence of a Lewis acid (Figure 1-25). This method was successively used to synthesis the difluorinated analogue of a Brassino steroid[92c].

61 **62**

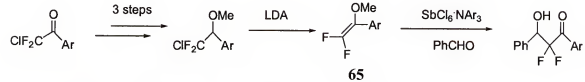
Figure 1-25. Brook rearrangement approach.

Similary, condensation of trifluoromethyltrimethylsilane (**63**) with acylsilane, catalysed by fluoride, gave silylenol ethers[93a-c] (**64**). Aldol reactions, alkylations, glycosylations and Michael reactions were performed with this silyenol ether under Lewis acid activation in one pot sequences (Figure 1-26). Reactions of the silyllithium and silylmagnesium reagents with trifluoromethyl ketones to give difluoro enol eilyl ethers also were reported, but the yields were relatively lower.[93d]



Conditions: a) $Bu_4NPh_3SnF_2$, THF, -78°C to –24°C; b) PhCHO, $TiCl_4$; c) $ZnBr_2$, PhCH(Me)Br; d) $ZnBr_2$, MeCOCl; e) $ZnBr_2$, CH_2=CHCOMe.
Figure 1-26. Formations and reactions of difluoro silylenol ethers.

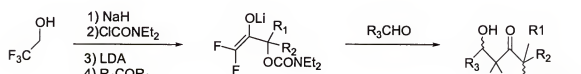
More stable difluoroenol ethers (**65**) were prepared from ethyl chlorodifluoroacetate in four steps by the Taguchi group (Figure 1-27).[94] In the presence of a Lewis acid, such as $SbCl_5$, $SbCl_6{}^-NAr_3$ or $Cu(OTf)_2$, difluorovinyl methyl ether reacted with carbonyl compounds to give O-methylated aldol-type products in good yields. Reaction of difluorovinyl methyl ether with N-acyliminium species in the presence of molecular sieves 4 Å provided β-amino-α,α-difluoroketone in good yield.



65

Figure 1-27. Formations and reactions of difluoroenol ethers.

Percy has prepared lithium enolates of difluoroketones from the acyl anion equivalent, which are available from the N,N-diethyl carbamate ester of trifluoroethanol[95] (**66**) (Figure 1-28). Reaction of the enolate with an aldehyde or ketone produced the lithium enolate, which recated with non-enolisable aldehydes to give highly functionalized aldol products in one pot with good yields.

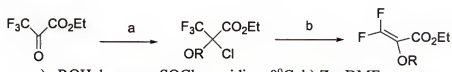


66

Figure 1-28. Formations and reactions of lithium enolates of difluoroketones.

Shi et al. reported reductive dechlorofluorination of α-chloro-α-alkoxy-β,β,β-trifluoropropionates to generate difluoro enol ether as difluoroenolates equivalents

(Figure 1-29). These difluoroenol ethers have been utilized to synthesize α,α-difluoro ketones, β-fluoro-α-keto acids and β,β,-difluoro-αamino acids.[73]



a) ROH, benzene, $SOCl_2$, pyridine, 0°C; b) Zn, DMF

Figure 1-29. Formation of difluoroenol ethers by reductive dechlorofluorination of α-chloro-α-alkoxy-β,β,β-trifluoropropionates.

Recently, Uneyama reported electrochemical reduction of n-hexyl trifluoroacetate to give α-trimethylsilyl-α,α-difluoroacetate (**67**), a stable and isolable alternative of difluoroketene alkyl silyl acetal (Figure 1-30).[96a,b] Reaction with benzaldhyde and benzyl bromide, benzoyl chloride gave corresponding products in good yields. 2,2-Difluoroenol silyl ethers and difluoroketene silyl (O,O-, O,S-, and O,N-) acetals were also successfully prepared by electroreductive defluorination of trifluoromethyl ketones and trifluoroacetic acid derivatives.[96c] N-TMS-β,β-Difluoroenamines were prepared from trifluoromethyl imines by electrochemical reduction and used for synthesis of difluoromethylene compounds[96e] (Figure 1-31). Magnesium promoted selective defluorination of trifluoromethyl ketones in the presence of TMSCl provided an easy method to prepare 2,2-difluoro enol silyl ethers[96d] (Figure 1-32).

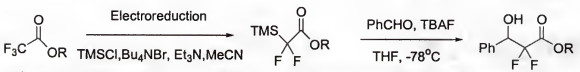


Figure 1-30. Formation of stable and isolable alternative of difluoroketene alkyl silyl acetals.

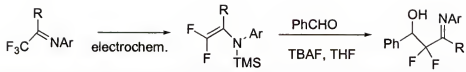


Figure 1-31. Formation of N-TMS-β,β-difluoroenamines by electrochemical reduction.

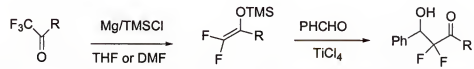


Figure 1-32. Magnesium promoted selective defluorination of trifluoromethyl ketones.

The lithium enolate of ethyl difluoroacetate has been investigated. However, this species is not stable and results in formation of a β-keto ester via a self-condensation reaction.[97] Weigel has published a route for the synthesis of α,α-difluoro-β-hydroxy esters through enolization of the precursor thioester (**68**) (Figure 1-33).[98] Also, difluoroketene silyl O,S-acetal can be generated by with the presence of trimethylsilane chloride. Moreover, difluoroketene dithioacetal has been observed to undergo nucleophilic attack by either alkyllithium or Grignard reagents.

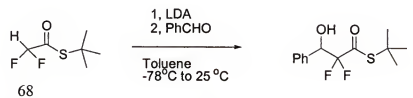


Figure 1-33. Formation and reaction of lithium enolate of ethyl difluoroacetate.

Finally, fluorinated enolates have been used to produce general synthon for further functionalisation. The difluorosilyl enol ether can be converted to any of the possible halodifluoromethyl ketones upon treatment with the appropriate electrophile

(NCS, NBS or ICl). Iododifluoromethyl ketones are a valuable class of intermediate; Qiu and Burton[99] have shown that they add efficiently to alkenes in the presence of catalytic palladium (0), or under photolysis conditions (Figure 1-34).

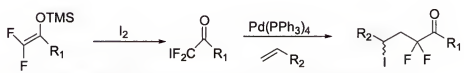
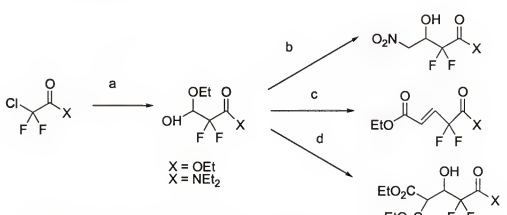


Figure 1-34. An example of the transformation of difluorinated enolates.

Formylation of the Reformatsky reagent derived from chlorodifluoroacetic acid provided the difluorinated hemiacetals, which were conveniently used as aldehyde equivalents (Figure 1-35).[100]



Conditions: a) Zn, DMF, $EtOSO_3Et$; b) CH_3NO_2, K_2CO_3;
c) $(EtO)_2POCH_2CO_2Et$, Et_3N; d) $CH_2(COOEt)_2$, ZnI_2 .

Figure 1-35. Formylation of the Reformatsky reagents.

Moreover, several fluorinated ketene thioacetals[101] have been reported and used in organic synthesis. Difluoroketene thioacetal (**69**), prepared from trifluoroactaldehyde thioacetal with LDA or alkyllithiums, has been shown to be useful as a building block for the preparation of α-monofluoroalkanoic acids[101a] (Figure 1-36). [3+2] Cycloaddition of

the nitrone with difluorodiphenylthioethylene (**70**) formed fluorinated isoxazolidines (Figure 1-37).[101c]

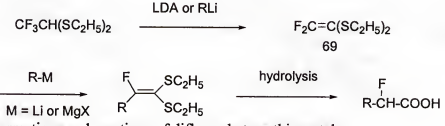


Figure 1-36. Formations and reactions of difluoro ketene thioacetals.

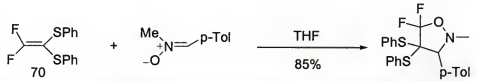


Figure 1-37. [3+2] Cycloaddition of the nitrone with difluorodiphenylthioethylene.

1.3.3 Monofluoroenolates and Perfluoroenolates

Study of monofluoroenolates can be traced back to the 1950s. Bergmann and co-workers[102,104] prepared α-fluoro enolates with no attempt to control the enolate geometry. Reformatsky reaction of ethyl α-bromo-α-fluoroacetate[103] and deprotonation of alkyl fluoroacetate[104] with different bases are the two major methods to generate α-fluoro enolates. t-Butyl fluoroacetate and 2,6-di-t-butyl-4-methyl-phenyl (BHT) fluoroacetate required treatment with LDA to form the enolate. Using LHMDS the lithium enolate of ethyl fluoroacetate was successfully generated. Fluoroacetamides were deprotonated with LDA and the amide enolate condensed with several aldehydes and ketones. Welch's account paper summarized all the aspects of mono fluoro enolates,[105]

such as the formation, reactivity of mono fluoro enolates, and specially the stereoselectivity outcomes of aldol reactions with mono fluoro enolates.

A perfluoroalkyl substituted ester enolate is expected to undergo rapid defluorination prior to trapping[105] (Figure 1-38). This defluorination would make formation of perfluoroalkyl substituted ketene silyl acetals difficult by this method.[106]

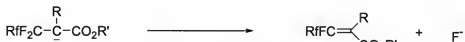


Figure 1-38. Defluorination of perfluoroalkyl substituted ester enolates.

However, Nakai has succeeded in the preparation of trifluoromethyl ketene silyl acetal from methyl trifluoromethylpropanoate.[107] Although use of lithium diisopropyl amide in THF at –78°C gave complete defluorination, triethylamine at room tempertaure with trimethylsilyl triflate as the trapping agent, gave the ketene silyl acetal in 92% NMR yield (E/Z = ¼) (Scheme 1-39). Further, Nakai and coworkers successfully developed a new practical method for the generating the parent ketone F-enolate from commercially available hexafluoroisopropyl alcohol (HFIP).[108] Perfluoroenolates, such as compound **71,** undergo both electrophilic and nucleophilic attack (Figure 1-40).

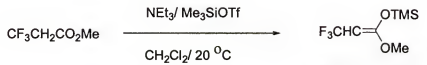


Figure 1-39. Preparation of trifluoromethyl ketene silyl acetal from methyl trifluoromethylpropanoate

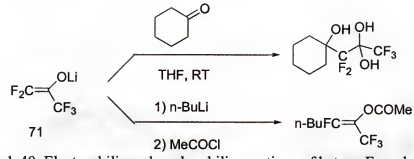


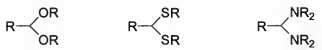
Figure 1-40. Electrophilic and nucleophilic reactions of ketone F-enolate.

In conclusion, difluoroenolates and their equivalents have been demostrated to be an attractive approach to the synthesis of difluoromethylene compounds. Two types of methods for the formation of such building blocks were widely used. They were Reformatsky-type reactions of halodifluoroacetate and halodifluoroketones, and selective defluorinations from a trifluoromethyl group. The successful cases of the selective demonofluorination were as base-catalyzed dehydrofluorination of a 2,2,2-trifluoroethyl group, chemical and electrochemical reductive defluorination of trifluoromethyl groups, Brook-type rearrangement of trifluoroacetylsilanes, reductive dechlorofluorination of α-chloro-α-alkoxy-β,β,β-trifluoropropionates, and reactions of silyllithium and silylmagnesium reagents with trifluoromethyl ketones.

CHAPTER 2
TRIFLUOROMETHYLATED AMINALS: SYNTHESIS AND UTILITY AS TRIFLUOROMETHYLATED BUILDING BLOCKS

2.1 Introduction

An aminal[109] is the aminated equivalent of an acetal, or a mercaptal and its functional group is characterized by the presence of two di- or mono-substituted amino groups on the same carbon atom (Figure 2-1). The preparation of aminals is usually through the condensation of carbonyl compounds with amines, substitution of dihalo compounds by amines, or addition of amines to iminium salts. The properties of aminals have been explored extensively, and they are summarized in several review articles.[110,111,112]



Acetal Mercaptal Aminal

Figure 2-1. General structures of acetal, mercaptal, and aminal

Aminals are versatile intermediates in classical organic chemistry, but they have rarely been used in organofluorine chemistry. Although several fluorinated aminal compounds, such as 1,1-bis(formamido)-2,2,2-trifluoroethane,[113] 1,1-bis(acetamido)-2,2,2-trifluoethane,[113] and a cyclic fluorinated aminal, 2-trifluoromethylimidazolidine,[50] have been made by the condensation of trifluoroacetaldehyde with amines, no further transformations were reported regarding synthetic applications of such compounds. Due

to the strong electron-withdrawing effect of the perfluoroalkyl group,[114,115] nucleophilic substitution at the position α to a perfluoroalkyl group generally occurs with difficulty except for sulfur nucleophiles,[116] which limits the preparation of fluorinated aminals. Successful syntheses of such compounds from commercially available fluorinated compounds would make it possible to explore the chemistry of trifluorinated aminals.

In contrast, fluorinated acetals have been widely used in fluorine chemistry, and several fluorinated dithioacetals (mercaptals)[101] have been prepared and used in organic synthesis. The synthesis and synthetic utilities of fluorinated acetals and mercaptals are summerized in Chapter **1**.

In this chapter, we report the facile preparation of trifluoromethylated aminals (**73**) from commercially available and inexpensive CF_3CHCl_2 (**72**) and their condensation reactions with ketones.

2.2 Results and Discussion

2.2.1 Synthesis of Trifluoromethyl Aminals

In 1994, Aoyama reported a facile synthesis of 1,1,1,4,4,4-hexafluoro-2-butene (HFC-356mff) from the inexpensive hydrochlorofluorocarbon 1,1,1-trifluoro-2,2-dichloroethane (HCFC-123) (**72**) by heating at 60°C with metallic copper in diethylamine[117] (Figure 2-2).

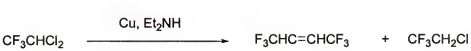


Figure 2-2. Preparation of 1,1,1,4,4,4-hexafluoro-2-butene.

We reproduced that result, and found a small but significant impurity, CF_3CH_2Cl, which proved very difficult to separate from HFC-356mff. In an attempt to further minimize this impurity, the reactions of CF_3CHCl_2 with a number of different secondary amines were examined (Table 2-1), and surprisingly we found that, among those tried, only diethylamine gave a respectable yield of HFC-356mff. Another major product was observed to be formed in the case of many of the alternative secondary amines, that being the respective 1,1-bis(dialkylamino)-2,2,2-trifluoroethanes **73a-e** (Figure 2-3). Without copper, the reaction did not occur. Also, at least three equivalents of amines were required to secure good yields.

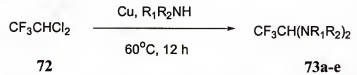


Figure 2-3. Preparation of trifluoromethylated aminals.

Table 2-1. Conversion of HCFC-123 to 1,1-Bis(dialkylamino)-2,2,2-trifluoroethanes **73**

Product	R_1	R_2	conditions	Yield (%)
73a	CH_3	CH_3	60 °C, 12 h	60
73b	-$(CH_2)_5$-		50 °C,12 h	57
73c	-$(CH_2)_2$-O-$(CH_2)_2$-		50 °C,12 h	52
73d	C_2H_5	C_2H_5	60 °C, 12 h	15
73e	-$(CH_2)_4$-		50 °C,12 h	55
	C_4H_9	C_4H_9	60 °C,12 h	-

Aminals, such as 1,1-bis(dialkylamino)-2,2,2-trifluoroethanes can easily be hydrolyzed to acetaldhydes under acid conditions. Thus, **73a** underwent hydrolysis in

10% HCl to give an 89% yield of the hydrate of trifluoroacetaldehyde. Therefore, these kind of aminal compounds should be able to be used as trifluoroacetaldehyde equivalents under appropriate conditions.

In an attempt to extend this methodology of aminal synthesis, reactions of CF_3CHCl_2 with several other types of amines were attempted under similar reaction condition. Ammonia, primary amines and aromatic amines did not give any desired aminal products even at higher reaction temperature, and dibenzylamine only gave 5% yield of product. Reaction of CF_3CHCl_2 with N,N'-dimethylethylenediamine gave only reductive product CF_3CH_2Cl with or without copper, and no desired cyclic aminal compound (**74**) was observed. Probably CF_3CHCl_2 act as an electron acceptor and diamine as electron donor in this reaction with the diamine undergoing fragmentation after single electron transfer as proposed below (Figure 2-4). Reaction with 1,3-N,N'-dimethylpropyldiamine gave 30% of cyclic aminal, 1,3-Dimethyl-2-trifluoro-hexahydro-pyrimidine (**75**). 1,3-Oxazolidine (**76-77**) having a trifluoromethyl group at the 2-position was made by this method, but the reaction gave relative low yield even with large excess of the amino-alcohols (Figure 2-5).

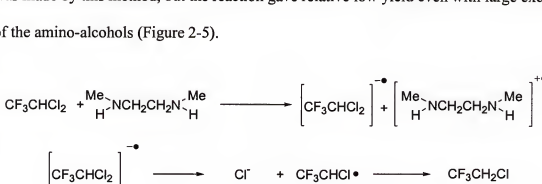


Figure 2-4. Proposed mechanism of the reaction of CF_3CHCl_2 with N,N'-dimethylethylenediamine.

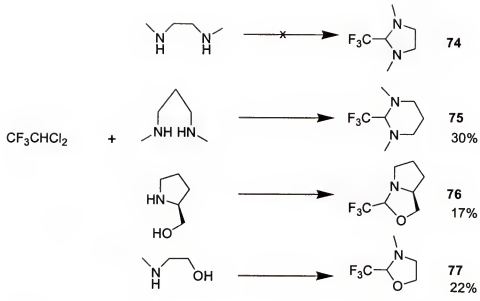


Figure 2-5. Preparations of trifluoromethylated cyclic aminals and O,N-acetals.

On the suggestion of Dr. Katritzky, synthesis of trifluoromethylated bisbenzotriazole (**78**) was attempted using this methodology. The reaction of CF_3CHCl_2 with benzotriazole in the autoclave gave no desired product, only the starting material was recovered. However, trifluoromethylated bisbenzotriazole was made by an alternative way as depicted in Figure 2-6. The condensation of trifluoroacetal hydrate with benzotriazole in the refluxing of benzene with azeotropic removal of water gave compound (**79**) (50%), directly treated with $SOCl_2$ in the presence of equivalent of benzotriazole gave the trifluoromethylated bisbenzotriazole compound (**78**). Presumably, the reaction proceeds through an initial compound (**80**), which can be isolated in 90% of yield by treating **79** with $SOCl_2$ without benzotriazole.

Another extension of the scope this reaction was attempted. Reaction of $CF_3CH_2CHCl_2$ with secondly amines, such as Me_2NH, piperidine, didn't give any products with the recovery of starting materials. Reaction of $CF_3CF_2CHCl_2$ with secondly

amines was expected to give similar chemistry, but its reaction gave a complicated mixtures containing several products, none of which appeared to be the desired aminal. In this latter example, the secondly amine probably acted as a base to eliminate HF, with the formation and further reaction of $CF_3CF{=}CCl_2$ giving complicated mixtures of products.

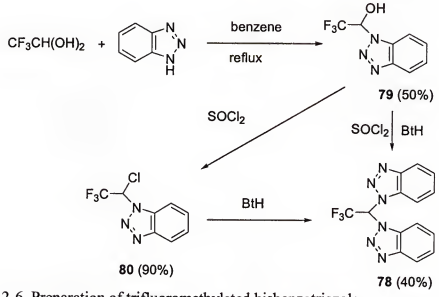


Figure 2-6. Preparation of trifluoromethylated bisbenzotriazole.

An extension of synthesis of unsymmetric aminals by aminal exchange failed to give a clean reaction. Thus, reaction of 1,1-bis(dimethylamino)-2,2,2-trifluoroethane with other amines in the presence of Lewis acid (ZnI_2, $TiCl_4$, $SnCl_4$, BF_3) gave a mixture of aminals from which it was difficult to isolate pure products.

2.2.2 Facile Synthesis of Trifluoromethyl Carbinols and Trifluoromethyl-α,β-unsaturated Ketones From the New CF_3CHO Synthetic Equivalent, 1,1-Bis(dimethylamino)-2,2,2-trifluoroethane

Trifluoroactaldehyde has always been recognized as a potentially very useful precursor to trifluomethyl carbinols.[40-45,118,119] However, because of its volatility, high

reactivity and commercial unavailability, trifluoroacetaldehyde almost never is used directly, rather it is usually generated in situ from its hydrate, hemiacetal, or acetal-type precursors, sometimes using Lewis acid catalysis.[55-63] Use of such methodology to generate a reactive electrophilic equivalent of CF_3CHO inevitably creates limitations with regard to the scope and effectiveness of its synthetic utility. Some of the useful applications are shown in Chapter **1**.

None of the previously reported CF_3CHO-equivalent methodologies has proved particularly useful for C-C direct bond-forming condensation reactions with ketones, an early report by Westheimer being typical (Figure 2-7).[120]

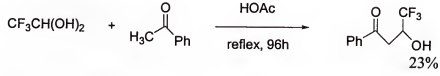


Figure 2-7. Condensation of trifluoroacetal hydrate with ketone.

Kubota has recently reported the use of silyl enol ethers to accomplish this overall conversion, although the reaction seems limited in utility with respect to aliphatic ketones[56] (Figure 2-8).

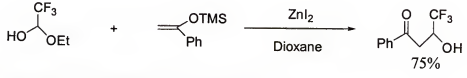
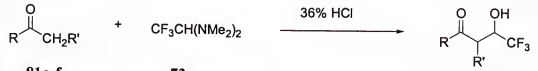


Figure 2-8. Reaction of TFAE with silyl enol ether.

1,1-Bis(dimethylamino)-2,2,2-trifluoroethane (**73a**), when treated with 36% aqueous HCl, acts as an effective *in situ* source of CF_3CHO in direct condensation

reactions with ketones **81a-f** (Figure 2-9), yielding trifluoromethyl carbinols **82a-f** in moderate to good yield (Table 2-2).



81a-f **73a** **82a-f**

Figure 2-9. Synthesis of trifluoromethyl carbinols.

Table 2-2. Reactions of 1,1-bis(dimethylamino)-2,2,2-trifluoroethane with ketones

Ketone	Conditions[b]	Major Product	Isomer Ratio	Yield(%)[a]
Acetone, 81a	reflux, 11h	82a: R=CH_3, R'=H	-	68
Acetophenone, 81b	EtOH, reflux,14h	82b: R= Ph, R'=H	-	46
3-pentanone, 81c	85 °C, 30 h	82c: R=C_2H_5, R'=CH_3	10 : 7[c]	43
Cyclohexanone,81d	80°C, 18h	82d: R, R'=$(CH_2)_4$	2.5 : 1[c]	51
2-pentanone, 81e	90°C, 22h	82e: R=C_3H_7, R'=H	100 : (4 : 3)[c]	63
2-butanone, 81f	90°C, 22h	82f: R=C_2H_5, R'=H	4 : (1 : 1)[c]	56

a. yields isolated by distillation; b, no solvent; c, mixture of diastereomers

In a typical procedure, 0.85g of $CF_3CH(NMe_2)_2$, 2.0g of cyclohexanone, and 0.5 mL of 36% HCl were heated at 80°C. After 18 hours, ^{19}F NMR spectrum showed that the starting material was consumed. The reaction was cooled, 20 mL of CH_2Cl_2 was added, and the mixture washed with brine, dried and distilled (50-53 °C at 0.03 mm Hg) to give 0.50g (51%) of a 2.5: 1 mixture of diastereomers, **82d**. No solvent was used in these reactions except for acetophenone , when EtOH was used.

In attempts to define the most advantageous conditions, optimization experiments were carried out using acetone as the model substrate. The reaction was found to proceed quite cleanly, but much more slowly, without acid (63% product from **81**a after refluxing in H_2O for 35 hours). However, using no water and ZnI_2, $SnCl_4$, or $BF_3 \bullet Et_2O$ as catalysts,

gave only complex mixtures of products. Using a larger excess of 36% HCl led to shorter reaction times, but at some sacrifice of yield (Table 2-3).

Table 2-3. Reaction of acetone with 1,1-bis(dimethylamino)-2,2,2-trifluoroethane

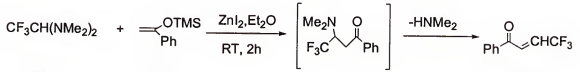
Reaction	Conditions	Time	Yield
1	Water, reflux	35 hours	63%
2	reflux under N_2	20 hours	No reaction
3	K_2CO_3, N_2, reflux	39 hours	No reaction
4	eq. 36% HCl, reflux	20 hours	68%
5	excess 36% HCl,reflux	11 hours	61%
6	ZnI_2/THF, reflux	4 hours	mixture
7	$SnCl_4/CH_2Cl_2$, RT	1 hour	complex
8	$BF_3{\cdot}Et_2O$, RT	2 hours	complex

Cyclohexanone and 3-pentanone gave a mixture of diastereomeric products, with little selectivity being exhibited. Unsymmetric ketones such as 2-butanone and 2-pentanone, reacted with significant regioselectivity, with a preference for the reaction at the methyl rather than the methylene site. In the case of 2-pentanone, a 14:1 preference for the formation of 1,1,1-trifluoro-2-hydroxy-4-heptanone, **82e** was observed.

2.2.3 Reaction with Silyl Enol Ethers

When silyl enol ethers were used in the reaction with aminal (**73a**), under anhydrous conditions using ZnI_2 as Lewis acid catalyst, the reaction proceeds directly to elimination products under the reaction conditions, presumably via an initial, amine-containing adduct, such as **84**, which can be detected in the crude product mixture. Complete conversion of **84** to

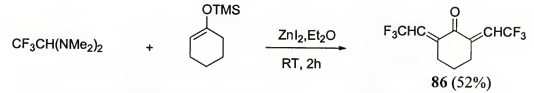
85[120] occurs during silica gel flash chromatography. A control experiment in which silica gel was added to the reaction mixture, directly give **85** before workup (Figure 2-10).



73a **83** **84** **85** (90%)

Figure 2-10. Reaction of aminal with silyl enol ether.

When the silyl enol ether of an aliphatic ketone is used in the reaction, a more complex product mixture is formed, with multiple substitution (**86**) dominating as shown below for cyclohexanone sily enol ether (Figure 2-11). Such results are reminiscent of these obtained by Kubota in his condensations of silyl enol ethers with trifluoroacetaldhyde hemiacetals.[56]



86 (52%)

Figure 2-11. Reaction of aminal with cyclohexanone sily enol ether.

In conclusion, trifluoromethylated aminals were successfully synthesized from commercially inexpensive reagent CF_3CHCl_2. 1,1-Bis(dimethylamino)-2,2,2-trifluoroethane (**73a**) was found to be a good trifluoroacetaldehyde synthetic equivalent, perhaps the best one for use in direct acid catalyzed condensation reactions with ketones to form β-keto trifluoromethylcarbinols of the general structure, $RCOCHR'CHOHCF_3$.

Silyl enol ethers were found to undergo a ZnI_2-catalyzed condensation with **73**a to form α,β-unsaturated products of the general structure, $CF_3CH=CR'COR$.

2.3 Experimental

1,1-bis(dimethylamino)-2,2,2-trifluoroethane, **73**a

A mixture of 1,1,1-trifluoro-2,2-dichloroethane (50g, 0.33mol) and copper powder (43g, 0.68mol) in an autoclave was cooled to -78°C, the air in the autoclave was removed under Vacuum. Then 100g of dimethylamine was transferred to the autoclave. The reaction mixture was allowed to warm to room temperature, and then heated at 60°C for 12 hours. After that the mixture was cooled to room temperature. The liquid was separated, and the solid was washed with 30 mL of methylene chloride. The liquid phase was combined and distillated to give 33.8g (60%) of 1,1-bis(dimethylamino)-2,2,2-trifluoroethane, b.p. 92-93°C.

^1H NMR ($CDCl_3$) δ 2.39 (q, 12H, J=1.2 Hz), 3.18 (q, 1H, J=7.3 Hz); ^{19}F NMR ($CDCl_3$) δ -67.00 (d, 3F, J=7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 41.3, 83.7 (q, J=26.2 Hz), 126.9 (q, J=293.6 Hz).; IR (neat) : 2821.5, 1688.4, 1474.6, 1381.4, 1259.7, 1140.0, 1066.7, 880.5, 714.4; MS: 170 (M+, 8.04), 126 (M+-44, 100), 101 (M+-69.88); HRMS Calcd for $C_6H_{13}F_3N_2$: 170.1031, Found 170.1052; Anal. Calcd for $C_6H_{13}F_3N_2$: C, 42.35; H, 7.65; N, 16.47. Found: C,42.43; H, 7.89; N, 16.30.

1,1-bis(diethylamino)-2,2,2-trifluoroethane, **73**d

A mixture of 1,1,1-trifluoro-2,2-dichloroethane (152g, 1 mol), diethylamine (150 mL) and copper powder (146g, 2.3 mol) in an autoclave was cooled to -78°C, the air in the autoclave was removed under vacuum. The reaction mixture was allowed to warm to room temperature, and then heated at 60°C for 12 hours. After that the autoclave was cooled to room temperature. 44g of mixture of 1,1,1,4,4,4-hexafluorobutene (44% based on 1,1,1-trifluoro-2,2-dichloroethane) and 1-chloro-2,2,2-trifluoroethane (5:1) (7% based on 1,1,1-trifluoro-2,2-dichloroethane) was collected in a trap which was cooled in dry ice-acetone. The residue was extracted with ethylene chloride (50 mL x 2). The extraction was distillated to 33.2g of 1,1-bis(diethylamino)-2,2,2-trifluoroethane (15% based on 1,1,1-trifluoro-2,2-dichloroethane), b.p. 70-72 °C/ 6 Torr.

^{1}H NMR δ 1.02 (t, 12H, J=7.1 Hz), 2.76 (m, 8H), 3.82 (q, 1H, J=7.8 Hz); ^{19}F NMR δ -67.80 (d, 3F, J=7.8 Hz); ^{13}C NMR δ 13.3, 43.3, 76.7 (q, J=16.6 Hz), 126.2 (q, J=292.1 Hz); IR (neat) : 2972.8, 1656.1, 1455.0, 1382.0, 1265.9, 1146.1, 1109.9, 1067.7, 988.2, 817.1, 714.8; HRMS Calcd for $C_{10}H_{21}F_3N_2$: 226.1657. Found 226.1670.

1,1-bis(piperidino)-2,2,2-trifluoroethane, **73**b

Yield: 57%; bp 125-127°C/ 6 Torr; ^{1}H NMR δ 1.40 (p, 4H, J=4.6 Hz), 1.52 (p, 8H, J=6.4 Hz), 2.73 (t, 8H, J=4.6 Hz), 3.21 (q, 1H, J=7.7 Hz); ^{19}F NMR δ -66.4 (d, 3F, J=7.3 Hz); ^{13}C NMR δ 24.6, 26.4, 50.7, 84.4 (q, J=26.4 Hz), 125.7 (q, J=293.6 Hz); IR (neat): 2911, 1681, 1445.1, 1388.9, 1257.9, 1114.5, 1008.4, 858.7, 833.8, 715.3; HRMS Calcd for $C_{12}H_{21}F_3N_2$: 251.1735. Found 251.1765; Anal. Calcd for $C_{12}H_{21}N_2F_3$: C, 57.60; H, 8.40; N, 11.20. Found: C, 57.34; H, 8.45; N, 11.31.

1,1-bis(morpholino)-2,2,2-trifluoroethane, **73c**

Yield 52%; bp 133-135°C / 6 Torr; ^{1}H NMR δ 2.69 (t, 8H, J=4.6 Hz), 3.22 (q, 1H, J=7.7 Hz), 3.59 (t, 8H, J=4.6 Hz); ^{19}F NMR δ -66.0 (d, 2F, J=7.3 Hz); ^{13}C NMR δ 49.5, 66.9, 83.2 (q, J=26.7 Hz), 125.1 (q, J=293.6 Hz); IR (neat): 2958.4, 1677.5, 1449.2, 1361.4, 1273.7, 1258.1, 1133.2, 1022.0, 881.6, 834.8, 717.7; HRMS Calcd for $C_{10}H_{17}O_2N_2F_3$: 255.1320. Found: 255.1315. Anal. Calcd for $C_{10}H_{17}O_2N_2F_3$: C, 47.24; H, 6.69; N, 11.02; Found C, 46.92; H, 7.17; N, 10.79.

1,1-bis(pyrrolidino)-2,2,2-trifluoroethane, **73d**

Yield: 55%; bp 107-108 °C / 6 Torr; ^{1}H-NMR δ 1.72 (p, 8H, J=3.2 Hz), 2.70 (m, 8H), 3.66 (q, 1H, J=6.8 Hz); ^{19}F-NMR δ -69.2 (d, 3F, J=7.3 Hz); ^{13}C NMR δ 23.8, 49.5, 78.0 (qd, J=27.7, 4.5 Hz), 125.7 (q, J=292.6 Hz); IR (neat): 2970.8, 2831.1, 1656.1, 1461.7, 1388.2, 1364.0, 1259.5, 1136.0, 890.4, 838.6, 714.4; HRMS Calcd for $C_{10}H_{17}F_3N_2$: 222.1344; Found 222.1393.

1,3-Dimethyl-2-trifluoro-hexahydro-pyrimidine, **75**

Yield: 30%; bp 180-182°C; ^{1}H-NMR 1.35 (dp, J = 4.2 Hz, 1H), 1.76-1.93 (m, 1H), 2.46 (q, J = 1.5 Hz, 6H), 2.50-2.60 (m, 2H), 2.86-2.99 (m, 2H), 3.54 (q, J = 8.1 Hz); ^{19}F-NMR –66.14 (d, J = 8.1 Hz); ^{13}C-NMR 18.83, 42.06 (q, J = 1.5 Hz), 49.97, 78.34 (q, J = 26.7 Hz), 125.95 (q, J = 295.1 Hz); HRMS (CI) Calcd. for $C_7H_{14}N_2F_3$ (M+1): 183.1109; Found: 183.1134.

3-Trifluoromethyl-tetrahydro-pyrrolo[1,2,c]oxazole, **76**

Yield: 17%; bp 165-167°C; ^{1}H-NMR 4.71 (q, J = 5.6 Hz, 1H), 4.14 (t, J = 7.6 Hz, 1H), 3.82 (m, 1H), 3.50 (m, 1H), 3.27 (dt, J = 10.0, 6.7 Hz, 1H), 2.83 (dt, J = 10.0, 6.8 Hz, 1H), 2.09 (m, 1H), 1.88 (p, J = 7.1 Hz, 2H), 1.67 (m, 1H). ^{19}F-NMR –81.63 (d, J = 6.4 Hz); ^{13}C 25.28, 29.92, 55.17, 63.47, 72.38, 94.47 (q, J = 33.2 Hz), 123.22 (q, J = 284.0 Hz); HRMS Calcd. for $C_7H_{10}ONF_3$: 181.0714; Found 181.0714.

3-Methyl-2-trifluoromethyl-oxazolidine, **77**

Yield: 22%; bp 121-123°C; ^{1}H NMR 2.58 (s, 3H), 2.76 (m, 1H), 3.28 (m, 1H), 3.99 (t, J = 6.4 Hz), 4.34 (q, J = 5.1 Hz); ^{19}F-NMR –81.69 (d, J = 5.1 Hz); ^{13}C-NMR 41.84, 54.53, 66.73, 92.94 (q, J = 33.1 Hz), 121.64 (q, J = 283.5 Hz); IR (neat): 2965.4, 2901.0, 2832.9, 2806.1, 1460.7, 1398.1, 1352.0, 1332.2, 1294.0, 1257.0, 1136.0, 1093.0, 1071.6, 1048.5, 965.4, 912.5, 866.0, 851.4, 707.6, 676.3, 609.0. HRMS (CI) Calcd. for $C_5H_9ONF_3$ (M+1): 156.0636; Found 156.0708.

1-Benzotriazol-1-yl-2,2,2-trifluoro-ethanol, **79**

Benzotriazole (1.2g, 10 mmol) was added to a solution of trifluoroactaldehyde hydrate (2.32g, 20 mmol) in benzene (50 mL), and the reaction mixture was refluxed for 12 hours using a Dean-Stark trap. ^{19}F NMR showed the products at -79.74 (d, J = 6.4 Hz), the crude product was used to further reaction without isolation. NMR Yield is calculated at around 50% (1.1g).

1-(1-chloro-2,2,2-trifluoro-ethyl)-1*H*-benzotriazole, **80**

Into above reaction mixture, thionyl chloride (1.5g, 15 mmol) wad added and the reaction mixture was refluxed for 2 hours. ^{19}F NMR spectra revealed the completion of reaction. After evaporation of solvents, the residue was purified by column chromatography to give white solid 1.1g (90%). The overall yield is 47%. mp 56-57°C; ^{1}H NMR 7.20 (q, J = 5.6 Hz, 1H), 7.48 (t, J = 7.3 Hz, 1H), 7.61 (t, J = 7.3 Hz, 1H), 7.82 (d, J = 8.3 Hz, 1H), 8.14 (d, J = 8.3 Hz, 1H). ^{19}F NMR –75.04 (d, J = 6.4 Hz, 3F) / -70.58 (d, J = 6.4 Hz, 3F) (24/1). ^{13}C NMR 67.28 (q, J = 40.8 Hz), 111.48 (q, J = 3.0 Hz), 120.78, 121.29 (q, J = 282.5 Hz), 125.30, 129.20, 131.13, 147.03. HRMS (CI) Calcd. for $C_8H_6N_3F_3Cl$: 236.0202; Found 236.0152; Anal. For $C_8H_5ClN_3F_3$: C, 40.85; H, 2.13; N, 17.87; Found: C, 40.84; H, 2.02; N, 17.70.

1,1-bis(Benzotriazol-1-yl)-2,2,2-trifluoroethane, **78**

Into above reaction mixture, thionyl chloride (1.7g, 15 mmol) and benzotriazole (1.2g, 10 mmol) were added and the reaction mixture was refluxed for 10 hours. ^{19}F NMR spectra revealed the completion of reaction. After evaporation of solvents, the residue was purified by column chromatography to give white solid 1.3g (overall yield 40%). Yield 80% ; mp 102-104°C; ^{1}H NMR 7.39 (t, J = 7.8 Hz, 2H), 7.53 (t, J = 8.3 Hz, 2H), 7.90 (d, J = 8.3 Hz, 2H), 8.07 (d, J = 8.3 Hz, 2H), 8.37 (q, J = 6.4 Hz, 1H). ^{19}F NMR –70.58 (d, J = 6.4 Hz, 3F)/ -58.99 (d, J = 6.4 Hz, 3F) (25/1). ^{13}C NMR 69.50 (q, J = 38.3 Hz), 110.25, 120.40, 121.49 (q, J = 285.5 Hz), 125.28, 129.45, 132.03, 145.95. HRMS (CI) Calcd. for $C_{14}H_{10}F_3N_6$ 319.0919; Found 319.0892; Anal. For $C_{14}H_9F_3N_6$: C, 52.83; H, 2.83; N, 26.42; Found: C, 53.49; H, 2.75; N, 26.09.

1,1,1-trifluoro-2-hydroxy-4-pentanone, **82**a

0.85g of 1,1-bis(dimethylamino)-2,2,2-trifluoroethane and 5mL of acetone were added in a 25mL flask, and then .05mL of 36% of HCl solution was added, and the reaction mixture was heated to reflux for 20 hours. ^{19}F NMR spectra showed that the starting material was gone. 10mL of water was added and solution was extracted with diethyl ether (3 X 20 mL), and dried with $MgSO_4$. After evaporation of solvent, the residue was distillated at reduced pressure to give 0.53 g of products (68%). b.p. 45-60°C/0.7 Torr; ^1H NMR δ 2.23 (s, 3H), 4.41-4.53 (m, 1H), 3.52-3.90 (br, 1H), 2.70-2.92 (m, 2H); ^{19}F NMR δ -80.12 (d, J=7.32Hz); ^{13}C NMR δ 30.62, 42.82, 66.30 (q, J=32.2 Hz) / 66.32 (q, J=32.2 Hz), 124.64 (q, J=280.5 Hz), 206.34. IR (neat) 3429.5, 2928.1, 1715.5, 1665.6, 1422.7, 1364.5, 1276.5, 1166.9, 1127.7, 1065.8, 875.9, 695.0, 546.1; HRMS (EI) Calcd. for $C_5H_7F_3O_2$: 156.0398. Found: 156.0488. Anal. For $C_5H_7F_3O_2$: C, 38.46; H, 4.49. Found: C, 38.14; H, 4.77.

1,1,1-trifluoro-2-hydroxy-4-phenyl-4-butanone, **82**b

Yield: 46%; m.p.: 90-92°C; ^1H NMR δ 3.25-3.48 (m, 2H), 3.80 (s, 1H), 4.72 (m, 1H), 7.50 (dd, J=7.97, 7.14 Hz), 7.64 (dd, J=7.42, 7.14 Hz), 7.97 (d, J=7.42 Hz). ^{19}F NMR δ -79.76 (d, J=7.33 Hz). ^{13}C NMR δ 38.26, 66.93 (q, J=32.2 Hz), 124.79 (q, J=280.5 Hz), 128.20, 128.85, 134.12, 135.97, 197.53. HRMS (EI) Calcd. for $C_{10}H_9F_3O_2$: 218.0555. Found: 218.0568. Anal. Cald. For $C_{10}H_9F_3O_2$: C, 55.05; H, 4.13. Found: C, 54.92; H, 4.13.

1,1,1-trifluoro-2-hydroxy-3-methyl-4-hexanone, **82**c

^{1}H and ^{13}C NMR was complex of three isomers. Yield: 43%; b.p. 63-65°C/ 2 Torr

^{19}F NMR δ -77.22(d, J=7.3 Hz);/ -77.60 (d, J=7.3 Hz) (7:10)

HRMS (EI) Calcd. for $C_7H_{12}O_2F_3$: 185.0789; Found: 185.0792.

IR (neat): 3451.4, 1712.8, 1270.1, 1173.1, 1136.7.

Anal. For $C_7H_{12}O_2F_3$: C, 45.65%; H, 5.98%. Found: C, 44.93%; H, 6.06%.

Reaction with cyclohexanone, **82**d

^{1}H and ^{13}C NMR was complex of three isomers. Yield: 51%; b.p. 40-53°C/ 0.03Torr.

^{19}F-NMR δ -76.21 (d, J=7.4 Hz)/ -76.35 (d, J=7.4 Hz) (1:2.5).

HRMS (EI) Cacld. for $C_8H_{12}F_3O_2$: 197.0789. Found: 197.0790.

IR (neat): 3450.6, 2946.9, 2868.7, 1708.0, 1452.8, 1452.8, 1430.6, 1347.8, 1277.8, 1167.8, 1127.1, 1068.6, 1033.9, 995.6. Anal. For $C_8H_{11}F_3O_2$: C, 48.98; H, 5.61. Found: C, 48.54; H, 5.85.

1,1,1-trifluoro-2-hydroxy-4-heptanone, **82**e

Yield: 63%; b.p. 73-77°C/ 2 Torr; ^{1}H NMR δ 0.92 (t, J=7.32Hz), 1.63 (Six, J=7.32 Hz), 2.46 (t, J=7.32 Hz), 2.77 (m,2H), 4.40-4.56 (m, 1H), 3.65-3.82 (m, 1H). ^{19}F NMR δ -80.07 (d, J=7.33 Hz). ^{13}C NMR δ 13.47, 16.90, 41.79, 45.53, 66.61 (q, J=32.2 Hz), 124.66 (q, J=280.5 Hz), 208.84. IR (neat) 3435.5, 2968.7, 2940.2, 1717.5, 1461.0, 1409.1, 1371.9, 1278.5, 1170.6, 1128.0, 1008.8, 900.0, 837.9, 693.9, 643.5. Elemt. Anal. For $C_7H_{11}F_3O_2$: C, 45.65; H, 6.01. Found: C, 44.69; H, 6.13. HRMS (EI) Calcd. for $C_7H_{11}F_3O_2$: 184.0711. Found : 184.0714.

1,1,1-trifluoro-2-hydroxy-4-hexanone, **82f**

^{1}H and ^{13}C NMR was complex of three isomers. Yield: 56%; b.p. 68-70°C/ 2 Torr

^{19}F NMR δ -77.21 (d, J=7.3 Hz)/ -77.25 (d, J=7.3 Hz)/ -80.11 (d, J=7.3 Hz). (1:1:4).

HRMS (EI) Calcd. for $C_6H_{10}O_2F_3$: 171.0633; Found: 171.0651.

1,1,1-trifluoro-4-phenyl-4-butenone, **85**

To a suspension of anhydrous zinc iodide (0.64g, 2mmol) in ether (20ml) at room temperature, 1,1-bis(dimethylamino)-2,2,2-trifluoroethane (0.34g, 2mmol) and was added. After stirring a few minutes, 1-phenyl-1-(trimethylsilyloxy)-ethylene (0.384g, 2mmol) was added. After the mixture was stirred at room temperature for two hours, diethyl ether (20ml) was added. The mixture was filtered, and the filtration was washed with brine (10ml x 2), dried with magnesium sulfate. After the solvent was evaporated, the residue was submitted to silica-gel column chromatography with hexane-ether acetate (10:1) to give product (0.36g, 90%).

^{1}H NMR ($CDCl_3$) δ 6.76-6.94 (m, 1H), 7.48-7.62 (m, 3H), 7.62-7.76 (1H), 7.94-8.06 (m, 2H). ^{19}F NMR ($CDCl_3$) δ -65.62 (d, J=4.9 Hz, 3F). ^{13}C NMR ($CDCl_3$) δ 122.54 (q, J=270.3 Hz), 128.78, 128.98, 129.99, 130.45, 130.03 (q, J=4.6 Hz), 134.11, 136.14, 187.97. IR: 3060.3, 1684.0, 1648.7, 1595.8, 1448.9, 1331.4, 1307.9. 1272.6, 1131.6, 1002.4, 967.1, 773.2, 696.8, 632.2. HRMS (EI) Calcd. for $C_{10}H_7OF_3$: 200.0449; Found: 200.0446.

2,6-bis(2,2,2-trifluoro-ethylidene)-cyclohexanone, **86**

The procedure was same as before. 0.34g (2mmol) of compound 1 and 0.17g (2mmol) of enol ether was used to give 0.27 g of product (52%) after chromatography with chloroform-hexane (1:4). ^{1}H NMR ($CDCl_3$) 1.87 (p, J=6.4 Hz, 2H), 2.88 (m, 4H), 6.66 (qt, J=8.7, 20 Hz, 2H). ^{19}F NMR ($CDCl_3$) -59.71 (d, J=9.7 Hz, 6F). ^{13}C NMR ($CDCl_3$) 20.36, 26.62, 122.95 (q, J=272.0Hz), 124.76 (q, J=34.8 Hz), 144.08 (q, J=5.0 Hz), 186.87. HRMS (EI) Calcd. for $C_{10}H_8F_6O$: 258.0479; Found 258.0513. Anal. Calcd. for $C_{10}H_8F_6O$: C: 46.51 H: 3.10; Found: C: 46.15 H: 2.90.

CHAPTER 3
SYNTHESIS OF TRIFLUOROMETHYLATED AMINES USING 1,1-BIS(DIALKYLAMINO)TRIFLUOROETHANES

3.1 Introduction

Trifluoromethylated compounds continue to be of great industrial interest,[118] and therefore the development of new methods to incorporate trifluoromethyl groups into organic compounds remains an important area of study. Among many building block approaches to trifluomethylated compounds, trifluoroacetaldehyde along with its derivatives are some of the most useful compounds and are used for the construction of functionalized trifluoromethylated components via reaction with a number of reagents.[6-8] The scope and effectiveness of the synthetic utility of trifluoroacetaldehyde and its derivatives are summarized in chapter **1**.

Aminals have been widely used as inexpensive and convenient reagents for the Mannich reaction,[121] as precursors of iminium ions. A number of methods have been developed for the preparation of dialkyl(methylene)iminium salts and their direct use in Mannich reactions. A special example of these iminium compounds is Eschenmoser's salt (**88**),[122] which can be very conveniently prepared *in situ* or preformed in aprotic solvents from N,N,N',N'-tetramethyldiaminomethane (**87**) and reactive acid derivatives such as acetyl chloride,[123] acetic anhydride,[124] chlorotrimethylsilane[125] etc (Figure 3-1).

87 **88**

Figure 3-1, Formation of Eschenmoser's salt.

In chapter **2**, we described the synthesis of triflouomethylated aminals and their synthetic use in the condensation reactions with ketones. In this chapter, we report the synthesis of a variety of trifluoromethylated amines using trifluoromethylated aminals as trifluoromethyl building blocks.

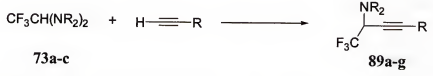
3.2 Results and Discussion

3.2.1 Preparation of Substituted Propargylamines from Aminals and Phenylacetylene in the Presence of Cu(I) I or ZnI_2

Komissarov[126] et al. reported that aminals derived from aromatic aldehydes could be heated with phenylacetylene and Cu(I) halides in acetonitrile to give propargylamines in good yields. The reactivity of trifluoromethylated aminals with phenylacetylene compounds under similar conditions was investigated (Figure 3-2). These reactions gave the expected products, trifluoromethylated propargylamines (**89a-g**), but the recations required longer times to finish, compared with nonfluorinated systems. Trifluoromethylated aminals reacted with phenylacetylene in one or two days, but required four days to react with alkyl acetylenes such as 1-hexyne to give only 50% conversion (Table 3-1).

Considering the reaction mechanism as Komissarov proposed[126] (Figure 3-3), the aminal acted as an HI acceptor, which led to the formation of copper phenylacetylide.

The formed iminium salt could then participate in an aminomethylation reaction with copper phenylacetylide. In order to improve the yield of the reaction, based on this proposal, the reaction of our trifluoromethylated aminal with phenylacetylene was tried using pyridine hydrobromide or methylamine hydrochloride as proton sources which could produce the desired iminium salts. However each reaction gave messy product mixtures. Also, other reagents (such as acetyl chloride, acetic anhydride, chlorotrimethylsilane) which had been successfully used in the preparation of performed iminium salts, were attempted, but all of these reactions gave messy product mixtures.



73a-c **89a-g**

NR_2 = dimethylamino (**73a**); NR_2 = piperidino (**73b**); NR_2 = morpholino (**73c**)
Conditions a: CuI, CH_3CN, reflux; Condition b: ZnI_2, THF, reflux.

Figure 3-2. Preparation of trifluoromethylated propargylamines.

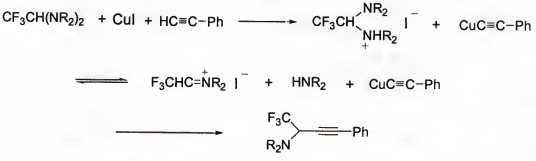


Figure 3-3. Proposed mechanism for the formation of trifluoromethylated propargylamines in condition A.

Using Lewis acids, trifluoroacetaldhyde N,O-acetals,[60] O,S-acetals[61] were reported to be successfully converted to the appropriate intermediate salts. Several

systems such as $SnCl_4$/1,2-dichloroethane, $TiCl_4/CH_2Cl_2$, BF_3/ether were tried to initiate the reaction of our trifluoromethylated aminal with phenylacetylene, but the reaction only worked with ZnI_2 as Lewis acid. When the reactions of 1,1-bis(dimethylamino)-2,2,2-trifluoroethane (**73**a) with phenylacetylene and 1-hexyne were performed using ZnI_2 as Lewis acid, the reaction proceeded faster and gave higher yields than that using CuI as shown in Table 3.1. Other trifluoromethylated aminals gave similar results. In the absence of other substrates, after 1,1-bis(dimethylamino)-2,2,2-trifluoroethane was refluxed with ZnI_2 in THF for 2 hours, ^{19}F NMR spectra showed two sets of fluorine signals at –66.9 ppm (starting material) and –74.3 ppm. The signal at –74.3 ppm is probably the trifluoromethylated iminium salt or the complex of aminal with ZnI_2. The mechanism of the reaction in the presence of ZnI_2 was proposed as shown in Figure 3-4. Formation of iminium salt by the reaction of **73**a with ZnI_2 is followed by electrophilic attack of phenylacetylene to form vinyl cation (**90**), and then loss of proton to give product **89**a. An alternative mechanism is similar to the case of CuI catalysis as shown in Figure 3-5. The reaction of **73a** with ZnI_2 formed iminium salt and zinc amide, the latter undergoes deprotonation to form alkynyl zinc. The reaction of intermediate, alkynyl zinc with iminium salt give the final product **89**.

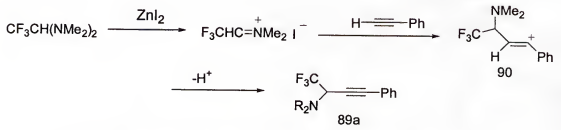


Figure 3-4. Proposed mechanism for the formation of trifluoromethylated propargylamines in condition B.

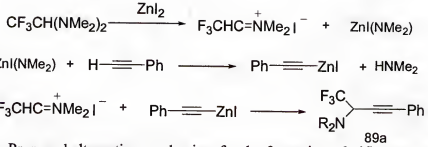


Figure 3-5. Proposed alternative mechanism for the formation of trifluoromethylated propargylamines in condition B.

Table 3-1. Preparation of substituted propargylamines from aminals and phenylacetylenes

compound	Aimials (NR_2)	Acetylene	Condition (time)	Yield
89a	dimethylamino	Phenyl	A (18 hrs)	64%
89a	dimethylamino	Phenyl	B (12 hrs)	77%
89a	dimethylamino	Phenyl	$TiCl_4/CH_2Cl_2$	complex
89b	dimethylamino	*1*-hexyne	B (20 hrs)	63%
89c	dimethylamino	*p*-methylphenyl	A (36 hrs)	55%
89d	piperidino	Phenyl	A (72 hrs)	54%
89e	piperidino	*p*-methylphenyl	B (31 hrs)	65%
89f	morpholino	Phenyl	A (4 days)	50% conversion
89g	morpholino	phenyl	B (48 hrs)	56%

Condition A: CuI, CH_3CN, reflux; Condition B: ZnI_2, THF, reflux.

In order to examine the scope of reaction, the reaction of 1,1-bis(dimethylamino)-2,2,2-trifluoroethane with diphenylacetylene was performed in THF in the presence of zinc iodide. However only starting material (diphenylacetylene) was recovered after refluxing for two days. Interestingly, refluxing of 1,1-bis(dimethylamino)-2,2,2-trifluoroethane with 1-phenyl-2-(trimethylsilyl)acetylene in ether in the presence of zinc iodide for three days gave a major product in 35% yield (Figure 3-6). The structure of the

product (**91**) was confirmed by ^{1}H, ^{19}F, ^{13}C NMR, MS spectra and elemental analysis. The mechanism for its formation is proposed as in Figure 3-7. The initially formed imminium salt reacts with phenyl-trimethylsilylacetylene to form vinyl cation **92**, which is stablized by the phenyl group and by the β-trimethylsilyl group. Intramolecular hydride transfer leads to intermediate **93**, which is converted to **91** upon workup hydrolysis. The failure of diphenylacetylene to react under the same conditions probably is due to steric effects, which prohibited the formation of the intermediate vinyl cation. However, reaction of trifluoromethylated aminal (**73c**) with 1-phenyl-2-(trimethylsilyl)acetylene under the same conditions failed to give desired product (**94**), probably due to the increased steric demand of this aminal (Figure 3-8).

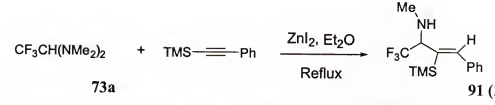


Figure 3-6. Reaction of trifluoromethylated aminal with phenyltrimethylsilylacetylene.

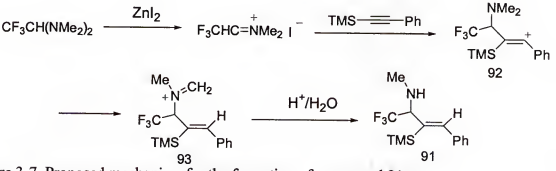
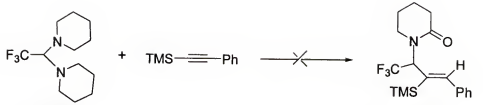


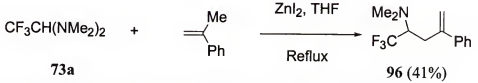
Figure 3-7. Proposed mechanism for the formation of compound **91**.



73c **94**

Figure 3-8. Attempted reaction of compound **73c** with phenyltrimethylsilylacetylene.

Also, the reactions of 1,1-bis(dimethylamino)-2,2,2-trifluoroethane with α-methyl styrene (**95**), styrene and 1-octene were carried out in the presence of ZnI_2. After refluxing the mixture for four days, α-methyl styrene gave 41% of product (**96**) along with some polymers (Figure 3-9). In the cases of styrene and 1-octene, similar treatment gave only polymers and no desired products. The structure of compound (**96**) was confirmed by ^{1}H, ^{19}F, ^{13}C NMR and MS spectral data. Thus, α-methyl styrene underwent reaction with the imminium salt to form a stabilized tertiary cation, which lost a proton to form **96**.



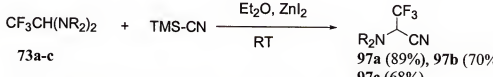
73a **96** (41%)

Figure 3-9. Reaction of trifluoromethylated aminal with α-methyl styrene.

3.2.2 Preparation of α-Trifluoromethylated α-Aminonitrile

Trifluoromethylated aminals (**73a-c**) reacted readily with cyanosilane in anhydrous ether at room temperature, under ZnI_2 catalysis (Figure 3-10). Analogous

carbon-carbon bond formation reactions using trifluoroacetaldehyde O,O-acetals,[56] N,O-acetals [60] and O,S-acetals[61] have already been reported. In the case of trifluoroacetaldehyde hemi acetal, the reaction required dioxane as a solvent. In our case, the reaction in ether, tetrahydrofuran or dioxane gave the same results. Generally, the reactions of trifluoroaldehyde N,O-acetals and O,S-acetals require stronger Lewis acids. The hydrolysis of cyano compounds under acid conditions provides a route to trifluoromethylated amino acids. [2c]



73a-c

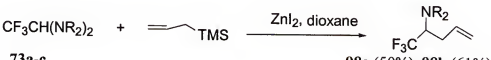
97a (89%), **97b** (70%)
97c (68%)

NR_2 =dimethylamino (**73a**); NR_2 = piperidino (**73b**); NR_2 =morpholino (**73c**)

Figure 3-10. Preparation of α-trifluoromethylated α-aminonitrile.

3.2.3 Reaction with Allyltrimethylsilane, Trimethylsilyacetylene and Propargylsilane

The reaction of trifluoro aminals with allytrimethylsilane in ether, THF or dioxane in the presence of zinc iodide gave the corresponding 1-trifluoromethylated homoallylic amines (**98**) in 50-60% yield (Figure 3-11).



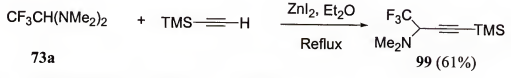
73a-c

98a (50%), **98b** (61%)
98c (58%)

NR_2 =dimethylamino (**73a**); NR_2 = piperidino (**73b**); NR_2 =morpholino (**74c**)

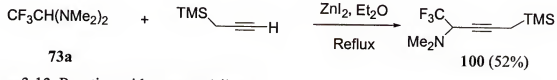
Figure 3-11. Reaction with allyltrimethylsilane.

The formation of allylic amines by the reaction of **73** with vinyltrimethylsilane did not occur under same conditions. However reaction with (trimethylsilyl)acetylene under the same condition gave 61% of product **99** (Figure 3-12). Normally, the 2-propynyltrimethylsilane reacts with electrophiles to form allenic structures.[127] Interestingly, reaction of 1,1-bis(dimethylamino)-2,2,2-trifluoroethane with 2-propynyltrimethylsilane in ether in the presence of zinc iodide gave 52% of product **100** (Figure 3-13). The reaction of trifluoromethylated aminal with both trimethylsilylacetylene and propargyltrimethylsilane gave same type of terminal H-substutution product as those shown in Table 3-1. The mechanism of this type of reaction probably followed the proposed in Figure 3-5, which is consistent with the retaining of TMS group in the products **99** and **100**.



73a **99** (61%)

Figure 3-12. Reaction with trimethylsilylacetylene.



73a **100** (52%)

Figure 3-13. Reaction with propargylsilane.

In conclusion, the reaction of **73** with allyltrimethylsilane in the presence of ZnI_2 gave the corresponding 1-trifluoromethylated homoallylic amines. Cyanotrimethylsilane reacted with **73** in the presence of ZnI_2 to give products of the general structure,

$CF_3CH(NR_1R_2)CN$. Lewis acid catalyzed deamination of **73** generates the 2,2,2-trifluoro-1,1-dialkylaminoethyl carbocation, which underwent electrophilic reaction with alkynes to give trifluoromethylated alkynylamines.

3.3 Experimental

1-phenyl-3-dimethylamino-4,4,4-trifluorobutyne, **89a**

Procedure (A) for the synthesis of trifluoromethylated propargylamine using CuI: A mixture of 1,1-bis(dimethylamino)-2,2,2-trifluoroethane (1.7g, 10mmol), phenylacetylene (1.02g, 10mmol), and CuI (1.9g, 10mmol) in 20 ml anhydrous acetonitrile was refluxed with stirring for 18 hours. After the mixture was cooled, filtered and solvent was evaporated and the residue was submitted to chlomatography with hexane-ether acetate (10:1) to give liquid products (1.3g, 64%).

Procedure (B) for the synthesis of trifluoromethylated propargylamine using ZnI_2: To a suspension of anhydrous zinc iodide (0.64g, 2mmol) in THF (10ml) at room temperature, 1,1-bis(dimethylamino)-2,2,2-trifluoroethane (0.34g, 2mmol) and phenylacetylene (0.25g, 2mmol) was added. The reaction mixture was refluxed with stirring overnight. ^{19}F NMR spectra showed that the starting material was gone after12 hours refluing, water (10ml) was added , and the mixture was extracted with ether (20ml x 3). The combined extraction was washed with brine (10ml x 2), and dried over $MgSO_4$. After evaporation of solvent, column chlomatography of the residue with hexane-ethyl acetate (10:1) to give product (0.35g, 77%).

^{1}H: 2.48 (s, 6H), 4.15 (q, J=7.6 Hz, 1H), 7.32-7.38 (m, 3H), 7.48-7.54 (m, 2H). ^{19}F: -72.36 (d, J=7.6 Hz, 3F). ^{13}C: 42.68, 60.36 (t, J=32.2 Hz), 77.21, 88.82, 121.78, 123.85 (q, J= 282.53 Hz), 128.34, 128.91, 131.98. IR: 2951.2, 2834.1, 2787.3, 2213.7, 1591.8, 1492.3, 1463.0, 1363.5, 1264.0, 1199.7, 1170.4, 1117.7, 1053.3, 989.0, 883.6, 830.9, 749.0, 708.0, 690.5, 602.7, 526.6. HRMS (CI) Calcd. for $C_{12}H_{13}NF_3$ (M+1): 228.1000; Found, 228.1060. Anal. Calcd. for $C_{12}H_{12}NF_3$: C, 63.44; H, 5.29; N, 6.17. Found, C, 63.05; H, 5.22; N, 6.32.

2-dimethylamino-3,3,3-trifluorooctyne, **89b**

Reaction was complete after 28 hours using procedure B. Yield 63%, bp: 120-122 °C/ 15mmHg. ^{1}H NMR ($CDCl_3$) δ 0.93 (t, J=7.0 Hz, 3H), 1.35-1.60 (m, 4H), 2.27 (td, J=7.0, 2.0 Hz, 2H), 2.37 (s, 6H), 3.89 (qt, J=7.6, 2.1 Hz, 1H). ^{19}F NMR ($CDCl_3$) δ -72.79 (d, J=9.7 Hz, 3F). ^{13}C NMR ($CDCl_3$) δ 13.49, 18.23, 21.84, 30.58, 42.54, 59.83 (q, J=31.2 Hz), 67.05, 89.68, 123.99 (q, J=282.0 Hz). IR: 2954.5, 2884.9, 2840.7, 2801.7, 2225.9, 1460.7, 1366.7, 1319.7, 1272.6, 1202.1, 1166.9, 1119.9, 1037.6, 879.0, 843.7, 702.7. HRMS (CI) Calcd. for $C_{10}H_{16}F_3N(M^{+}+1)$: 207.1235; Found: 207.1250.

1-p-methylphenyl-3-dimethylamino-4,4,4-trifluorobutyne, **89c**

Reaction was complete after 36 hours using procedure A. Yield: 55%. ^{1}H: 2.07 (s, 3H), 2.33 (s, 6H), 4.00 (q, J=7.6 Hz), 1H), 6.89 (d, J=7.9 Hz, 2H), 7.44 (d, J=7.9 Hz, 2H). ^{19}F: -71.89 (d, J=7.3 Hz, 3F). ^{13}C: 21.21, 42.54, 60.63 (q, J=32.2 Hz), 77.31, 89.48, 119.29, 124.75 (q, J=282.0 Hz), 129.36, 132.21, 139.16. IR: 2953.8, 2879.9, 2837.6, 2793.3, 2224.6, 1610.3, 1504.6, 1457.1, 1356.7, 1314.4, 1268.9, 1169.8, 1119.1, 1053.6, 1033.2, 989.6, 877.4, 816.7, 688.1, 528.3. HRMS (EI) Calcd. for

$C_{13}H_{14}NF_3$: 241.1078; Found, 241.1056. Anal. For $C_{13}H_{14}F_3N$: C, 64.70; H, 5.81; N, 5.81. Found: C, 64.72; H, 5.82; N, 5.28.

1-phenyl-3-piperidino-4,4,4-trifluorobutyne, **89d**

Reaction was complete after 40 hours using procedure A. Yield: 54%. bp: 135-137 °C/3.5 mmHg. ^{1}H: 1.38 (p, J=5.6 Hz, 2H), 1.51-1.64 (m, 4H), 2.53-2.64 (m, 2H), 2.65-2.76 (m, 2H), 4.02 (q, J=7.8 Hz, 1H), 7.21-7.31 (m, 3H), 7.38-7.46 (m, 2H). ^{19}F: -71.63 (d, J=9.7 Hz). ^{13}C: 23.90, 26.11, 51.81, 60.97, (q, J=32.1 Hz), 78.40, 88.25, 121.99, 124.02 (q, J=282.9 Hz), 128.30, 128.77, 131.95. HRMS (EI) Calcd. for $C_{15}H_{16}NF_3$: 267.1235; Found: 267.1253. IR: 2927.8, 2857.5, 2822.4, 2225.4, 1597.7, 1492.2, 1443.1, 1390.2, 1343.2, 1318.1 1262.2, 1173.6, 1131.1, 1111.6, 1066.2, 1000.7, 985.1, 756.6, 690.5.

1-p-methylphenyl-3-piperidino-4,4,4-trifluorobutyne , **89e**

Reaction was complete after 30 hours using procedure B. Yield: 65%. bp: 120-122°C/3.5 mmHg. ^{1}H: 1.44 (p, J=5.6 Hz, 2H), 1.58-1.72 (m, 4H), 2.35 (s, 3H), 2.60-2.69 (m, 2H), 2.72-2.83 (m, 2H), 4.07 (q, J=7.6 Hz, 1H), 7.13 (d, J=7.9 Hz, 2H), 7.37 (d, J=7.9 Hz, 2H). ^{19}F: -71.66 (d, J=7.6 Hz, 3F). ^{13}C: 21.46, 23.91, 26.12, 51.78, 60.97 (q, J=25.7 Hz), 77.64, 88.37, 118.90, 124.04 (q, J=283.0 Hz), 129.04, 131.86, 138.97. HRMS (CI) Calcd. for $C_{16}H_{19}NF_3$ (M+1): 282.1470, Found: 282.1469. Anal. For $C_{16}H_{18}F_3N$: C, 68.33; H, 6.41; N, 4.98. Found: C, 68.10; H, 6.62; N, 5.16.

1-phenyl-3-morpholino-4,4,4-trifluorobutyne, **89f**

Reaction was complete after 48 hours using procedure B. Yield 56%.

^{1}H NMR ($CDCl_3$) δ 2.60-2.72 (m, 2H), 2.72-2.82 (m, 2H), 3.69 (t, J=4.4 Hz, 4H), 4.00 (q, J=7.4 Hz, 1H), 7.23-7.32 (m, 3H), 7.38-7.46 (m, 2H). ^{19}F NMR ($CDCl_3$) δ -71.79 (d, J=7.3 Hz, 3F). ^{13}C NMR ($CDCl_3$) δ 50.67, 60.52 (q, J=32.1 Hz), 66.86, 77.24, 89.02, 121.56, 123.71 (q, J=281.7 Hz), 128.34, 128.99, 131.95. IR: 2964.8, 2918, 2859.1, 2228.5, 1490.3, 1455.5, 1385.0, 1353.1, 1320.9, 1253.8, 1188.6, 1161.8, 1116.5, 1073.1, 1029.3, 1015.7, 935.9, 875.9, 842.4, 757.7, 704.2; HRMS (EI) Calcd. for $C_{14}H_{14}ONF_3$: 269.1027; Found: 269.1027.

1-phenyl-2-trimethlsilyl-3-methylamino-4,4,4-trifluoro-1-butene, **91**

To a suspension of anhydrous zinc iodide (0.64g, 2mmol) in ether (10ml) at room temperature, 1,1-bis(dimethylamino)-2,2,2-trifluoroethane (0.34g, 2mmol) and 1-phenyl-2-(trimethylsilyl)acetylene (0.35g, 2mmol) was added. The mixture was refluxed for 48 hours. ^{19}F NMR spectra showed that the starting material was gone. After reaction mixture was cooled to room temperature, ether (20mL) was added, and filtered. The filtration was washed with brine (10mL x 2), and dried with $MgSO_4$. After the solvent was removed, the residue was chromatographed on silica gel. Elution with hexane-ethyl acetate (10:1) gave colorless liquid 0.2g (35%).

^{1}H NMR ($CDCl_3$) δ 0.015 (s, 9H), 2.53 (s, 3H), 3.82 (q, J=7.3 Hz, 1H), 7.18-7.24 (m, 2H), 7.28-7.38 (m, 3H), 7.65 (m, 1H). ^{19}F NMR ($CDCl_3$) δ -72.94 (d, J=7.3 Hz, 3F). ^{13}C NMR ($CDCl_3$) δ 0.33, 34.60, 64.20 (q, J=27.5 Hz), 125.88 (q, J=282.9 Hz), 127.52, 127.87, 128.37, 137.39, 139.30, 146.40. IR:3354.1, 2954.5, 2895.7, 2813.6, 1590.0,

1490.1, 1443.1, 1354.9, 1255.0, 1155.1, 1125.7, 1108.1, 1037.6, 890.7, 843.7, 755.6, 696.8. HRMS (CI) Calcd for $C_{14}H_{21}NSiF_3$ (M^++1): 288.1395; Found: 288.1395. Anal. Calcd for $C_{14}H_{20}NSiF_3$: C, 58.54% N, 4.88% H, 6.97%; Found: C, 58.84% N, 5.03% H, 7.18%.

2-phenyl-4-dimethylamino-5,5,5-trifluoro-pentene, **96**

To a suspension of anhydrous zinc iodide (0.64g, 2mmol) in a solution of α-methylstyrene (0.24g, 2mmol) in ether (10ml) at room temperature, 1,1-bis(dimethylamino)-2,2,2-trifluoroethane (0.34g, 2mmol) and was added. After a few min. of stirring at room temperature the mixture was refluxed for 3 days. ^{19}F NMR spectra showed that the starting material was consumed. After cooling, the mixture was filtered, and the solvent was evaporated to give white residue which was chromatographed on silica gel. Elution with chloroform-hexane (1:10) gave product (0.2g, 41%). ^1H NMR 2.29 (s, 6H), 2.66-2.82 (m, 2H), 2.92-3.08 (m, 1H), 5.08 (s, 1H), 5.23 (s, 1H), 7.16-7.32 (m, 5H). ^{19}F NMR -69.34 (d, J=7.3 Hz, 3F). ^{13}C NMR 32.21, 40.99, 62.95 (q, J=26.7Hz), 115.48, 127.43 (q, J=291.6 Hz), 126.35, 127.61, 128.43, 140.15, 144.81. IR:3084.2, 2932.7, 2801.7, 1729.0, 1684.4, 1632.5, 1599.8, 1494.6, 1455.1, 1382.7, 1260.9, 1178.2, 1146.5, 1113.5, 1027.2, 953.5, 901.5, 852.6, 778.0, 701.2. HRMS (EI) Calcd. for $C_{13}H_{16}F_3N$: 243.1235; Found: 243.1238.

2-Dimethylamino-3,3,3-trifluoro-propanitrile, **97a**

To a suspension of anhydrous zinc iodide (3.2g, 10mmol) in ether (10ml) at room temperature, 1,1-bis(dimethylamino)-3,3,3-trifluoroethane (1.7g, 10mmol) and

cyanotrimethylsilane (1.14g, 10mmol) were added. The mixture was stirred at room temperature for two hours. Ether (20ml) was added, and filtered. The filtration was washed with brine (10ml x 2), and dried with $MgSO_4$. After the solvent was removed, the residue was distilled at reduced pressure to give colorless liquid (1.35g, 89%). bp: 70-72 °C/ 80mmHg. ^{1}H NMR ($CDCl_3$) δ 2.47 (s, 6H), 4.12 (q, J=7.3 Hz, 1H). ^{19}F NMR ($CDCl_3$) δ -71.09 (d, J=7.3 Hz, 3F). ^{13}C NMR ($CDCl_3$) δ 42.98, 60.63 (q, J=7.1 Hz), 109.90, 121.69 (q, J=280.1 Hz). IR: 2978.0, 28957, 2848.7, 2801.7, 1648.7, 1460.7, 1360.8, 1313.8, 1260.9, 1208.0, 1178.6, 1131.6, 1061.1, 1043.5, 943.6. HRMS (EI) Calcd. for $C_5H_7N_2F_3$: 152.0561; Found: 152.0597.

2-morpholino-3,3,3-trifluoro-propanitrile, **97c**

Reaction procedure was same as above. Yield: 68%. bp: 100-102°C/ 12mmHg. ^{19}F NMR ($CDCl_3$): -70.42 (d, J=7.3 Hz). ^{1}H NMR ($CDCl_3$): 2.65-2.73 (m, 2H), 2.78-2.88 (m, 2H), 3.77 (m, 4H), 4.11 (q, J=7.3 Hz, 1H). ^{13}C NMR ($CDCl_3$): 50.87, 60.24 (q, J=33.7 Hz), 66.24, 109.87, 121.61 (q, J=283.0 Hz). IR: 2972.6, 2925.5, 2864.7, 2257.8, 1458.0, 1388.9, 1356.7, 1318.3, 1299.8, 1256.8, 1200.9, 1171.7, 1116.5, 1074.1, 1017.7, 1032.9, 937.4. HRMS Calcd. for $C_7H_9ON_2F_3$: 194.0677; Found: 194.0665.

2-pipridino-3,3,3-trifluoro-propanitrile, **97b**

Reaction procedure was same as above. Yield: 70%. bp: 82-84°C/ 12 mmHg ^{19}F NMR ($CDCl_3$) δ -70.44 (d, J=7.3 Hz, 3F). ^{1}H NMR ($CDCl_3$): 1.49 (p, J=5.7 Hz, 2H), 1.60-1.70 (m, 4H), 2.55-2.65 (m, 2H), 2.71-2.82 (m, 2H). 4.05 (q, J=7.3 Hz, 1H). ^{13}C NMR ($CDCl_3$): 23.25, 25.62, 52.21, 60.99 (q, J=33.2 Hz), 110.39, 121.84 (q, J=283.1

Hz). IR: 2946.5, 2859.8, 2824.0, 2256.0, 1650.1, 1471.3, 1455.8, 1396.5, 1347.2, 1258.4, 1140.0, 1007.3, 941.3, 854.0, 812.6, 788.6, 757.8, 715.9, 690.7, 627.2, 537.0. HRMS (EI) Calcd. for $C_8H_{11}N_2F_3$: 192.0874, Found: 192.0873.

4-piperidino-5,5,5-trifluoro-1-pentene, **98b**

To a suspension of anhydrous zinc iodide (3.2g, 10mmol) in ether (10ml) at room temperature, 1,1-bis(piperidino)-2,2,2-trifluoroethane (2.5g, 10mmol) and allyltrimethylsilane (1.14g, 10mmol) were added. The mixture was stirred at reflux for overnight. Ether (20ml) was added, and filtered. The filtration was washed with brine (10ml x 2), and dried with $MgSO_4$. After the solvent was removed, the residue was distilled at reduced pressure to give colorless liquid 1.2g (58%). bp: 80-82°C/ 6mmHg. ^1H NMR ($CDCl_3$): 1.40-1.58 (m, 6H), 2.25-2.50 (m, 2H), 2.52-2.62 (m, 2H), 2.78-2.89 (m, 2H), 2.94-3.08 (m, 1H), 5.77-5.94 (m, 1H), 5.03-5.16 (m, 2H). ^{19}F NMR ($CDCl_3$): -69.36 (d, J=7.3 Hz). ^{13}C NMR ($CDCl_3$): 24.72, 26.89, 30.38 (q, J=1.5 Hz), 50.43, 65.97 (q. J=24.7 Hz), 116.62, 127.24 (q, J=292.1 Hz), 134.87. IR: 3081.7, 2937.3, 2863.0, 2824.1, 1697.4, 1643.9, 1469.4, 1454.6, 1443.3, 1419.2, 1393.5, 1360.2, 1325.9, 1272.4, 1248.2, 1208.9, 1156.6, 1116.7, 1065.9, 1033.4, 989.2, 916.2, 861.0, 848.0, 708.8. HRMS (EI) Calcd. for $C_{10}H_{16}NF_3$: 207.1235; Found: 207.1233.

4-dimethylamino-5,5,5-trifluoro-1-pentene, **98a**

Reaction procedure was same as above. Yield: 50%. Bp: 100-102°C. ^1H NMR: 2.33-2.43 (m, 2H), 2.43 (q, J=1.2 Hz, 6 H), 3.01-3.15 (m, 2H), 5.06-5.20 (m, 2H), 5.74-5.90 (m, 2H). ^{19}F NMR: -69.46 (d, J=7.3 Hz, 2F). ^{13}C NMR: 30.28 (q, J=2.0 Hz), 41.08, 64. 96 (q, J=24.7 Hz), 116.99, 127.27 (q, J=291.1 Hz), 134.50. IR: 3083.2,

2945.6, 2875.8, 2842.8, 2802.9, 1644.8, 1456.4, 1379.8, 1308.3, 1261.7, 1197.7, 1116.0, 1066.7, 1028.2, 993.8, 917.6, 848.0.

4-Morpholino-5,5,5-trifluoro-1-pentene, **98b**

Reaction procedure was same as above. Yield: 61%. bp: 89-91°C/ 6mmHg. ^{1}H NMR ($CDCl_3$): 2.29-2.51 (m, 2H), 2.62-2.72 (m, 2H), 2.84-2.94 (m, 2H), 2.97-3.12 (m, 1H), 3.58-3.71 (m, 4H), 5.07-5.19 (m, 2H), 5.77-5.93 (m, 1H). ^{19}F NMR ($CDCl_3$): -69.71 (d, J=7.3 Hz). ^{13}C NMR ($CDCl_3$): 29.93, 49.65, 65.42 (q, J=25.2 Hz), 67.65, 117.23, 126.84 (q, J=291.1 Hz), 134.17. IR: 3081.5, 2960.9, 2894.7, 2855.8, 1644.1, 1455.3, 1378.2, 1365.1, 1325.2, 1300.4, 1276.4, 1257.2, 1234.5, 1159.3, 1119.1, 1050.4, 994.7, 919.4, 853.8, 712.5. HRMS (EI) Calcd. for $C_9H_{14}F_3NO$: 209.1027. Found: 209.1076.

1-trimethylsilyl-3-dimethylamino-4,4,4-trifluorobutytyne, **99**

To a suspension of anhydrous zinc iodide (1.6g, 5mmol) in THF (10ml) at room temperature, 1,1-bis(dimethylamino)-2,2,2-trifluoroethane (0.85g, 5mmol) and (trimethylsilyl)acetylene (0.52g, 5 mmol) was added. The mixture was heated with stirring at 50 °C for 2 days. Then the reaction mixture was transferred at reduced pressure into a dry ice/acetone-cooled receiving flask (25mL, round bottom). After evaporation of solvent, the residue was distilled at reduced pressure to give colorless liquid (0.59g, 61%). Bp: 87-90°C/ 110mmHg. ^{1}H NMR ($CDCl_3$) δ 0.21 (s, 9H), 2.38 (s, 6H), 3.91 (q, J=7.5 Hz, 1H). ^{19}F NMR ($CDCl_3$) δ -72.47 (d, J=7.3Hz, 3F). ^{13}C NMR ($CDCl_3$) δ -0.23, 42.54, 60.38 (q, J=31.7 Hz), 92.77, 94.56, 123.63 (q, J=282.5 Hz). IR: 2955.8, 2870.1,

2827.2, 2795.1, 2173.6, 1454.7, 1449.3, 1411.8, 1358.2, 1310.0, 1267.1, 1251.1, 1197.5, 1170.7, 1122.5, 1052.9, 1052.1, 1015.4, 854.6, 763.6, 726.1, 693.9, 672.5, 618.9. HRMS (CI) Calcd. for $C_9H_{17}NF_3Si$ (M^++1): 224.1082; Found: 224.1014.

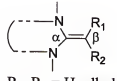
1-(trimethylsilyl)-4-dimethylamino-5,5,5-trifluoro-2-petanyne, **100**

To a suspension of anhydrous zinc iodide (1.6g, 5mmol) in THF (10ml) at room temperature, 1,1-bis(dimethylamino)-2,2,2-trifluoroethane (0.85g, 5mmol) and propargytrimethylsilane (0.56g, 5mmol) was added. The mixture was heated at 55 °C for overnight, ^{19}F NMR spectra showed that the reaction was finished. After reaction mixture was cooled to room temperature, ether (20mL) was added, and filtered. The filtration was washed with brine (10mL x 2), and dried with $MgSO_4$. After the solvent was removed, the residue was distilled at reduced presuure to give colorless liquid 0.2g (52%). Bp: 75-77°C/15mmHg. ^1H NMR 0.12 (s, 9H), 1.55 (d, J=2.44 Hz, 2H), 2.37 (s, 6H), 3.89 (qt, J=7.3, 2.4 Hz, 1H). ^{19}F NMR –72.91 (d, J=7.3 Hz, 3F). ^{13}C NMR –2.15, 6.99, 42.57, 60.00 (q, J=31.7 Hz), 66.63, 87.66, 124.12 (q, J=282.0 Hz). IR: 2958.1, 2878.3, 2837.8, 2792.1, 2215.7, 1460.4, 1413.5, 1364.4, 1317.9, 1270.2, 1252.0, 1198.0, 1169.5, 1114.4, 1037.4, 854.2, 761.8, 711.6. HRMS(EI) Calcd. For $C_{10}H_{18}NF_3Si$: 237.1161; Found: 237.1217. Anal. For $C_{10}H_{18}NF_3Si$ Calcd.: C, 50.63 H, 7.59 N, 5.91. Found: C, 50.55 H, 7.50 N, 5.93.

CHAPTER 4
DIFLUORO KETENE AMINAL: SYNTHESIS AND REACTIVITY

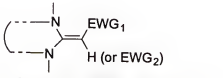
4.1 Introduction

Ketene aminals, also known as 1,1-enediamines or ketene N,N-acetals, are member of the enamine family.[128] In contrast to enamines, the chemistry of 1,1-enediamines has been only briefly studied although the earliest reports of such compounds may date back to the 1940s.[129,130] This has been partly due to the relative difficulty of the synthesis of simple 1,1-enediamines (**101**). Since more convenient methods have now been developed for the synthesis of this type of compound,[131,132] much attention has been given to them for further synthetic purpose.[128]



R_1, R_2 = H, alkyl

101



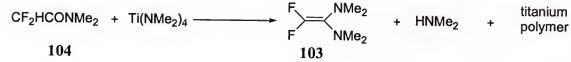
EWG_1, EWG_2 =COR, CO_2R, NO_2, CN etc.

102

With two amino groups attached to a single carbon atom of a double bond, 1,1-enediamines display some intriguing physical and chemical properties. One marked feature of these species is their enhanced enaminic reactivity. The nucleophilicity of the β-carbon atom is higher than that of the nitrogen atoms of primary and secondary amino

moieties. In addition, the double bond of a 1,1-enediamine is highly polarized. X-ray diffraction analysis of some compounds **102** have shown that the length of the double bond is longer than that of normal olefins (1.38-1.47 Å).[128,133-135] The double-bond character of these compounds is diminished with a concomitant reduction of their reactivity toward reduction and cycloaddition reactions. Furthermore, the amino substituents can also participate in reactions of this system by acting as either the nucleophilic site or as a leaving group. Therefore, 1,1-enediamines have been used as dinucleophiles or dipolar reagents in reactions with electron-deficient reagents to give products that are difficult to synthesize by other methods via a sequence of nucleophilic addition or substitution and cyclocondensation reactions of these species. The chemistry of the hydrocarbon ketene aminal system has been reviewed recently.[128]

Although ketene aminals have been used as versatile intermediates in classical organic chemistry, their fluorinated analogs have been only rarely used in organofluorine chemistry. Difluoroketene aminal **(103)** has been known for a long time,[136] having been made from $Ti(NMe_2)_4$ and N,N-dimethyl 2,2-difluoroacetamide **(104)** (Figure 4-1) however no pertinent chemistry was mentioned.

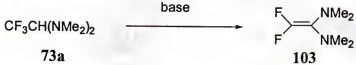


104 **103**

Figure 4-1. An early procedure for the preparation of difluoroketene aminal.

In view of considerable precedent, it seemed probable that compounds 73a-e could be used as precursors to prepare a series of potentially very useful fluorinated

"enolate" building blocks. As described in chapter 1, regents of a similar nature to **103** have attracted much interest because of their amibiphilic character, which allows them to exhibit either nucleophilic or electrophilic character in their reactions. Compound **73a** undergoes elimination of hydrogen fluoride upon treatment with base to form difluoro ketene aminal **103**(Figure 4-2).



73a **103**

Figure 4-2. Preparation of difluoroketene aminal.

4.2 Results and Discussion

4.2.1 Synthesis of Difluorinated Ketene Aminal

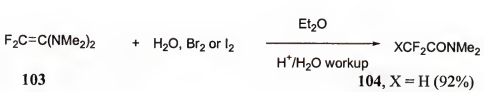
Treatment of **73a** (in ether, THF, or hexane) with 1.1 equivlent of n-BuLi (2.5 M in hexane) at –78 °C (or 0°C) under dry nitrogen, followed by warming to room temperature where it was allowed to stir for 10 hours, leads to greater than 90% conversion to **103**. The ^{19}F NMR spectrum of the resulting reaction mixture show a signal in the CF_2 group of **103** is at –114.10 ppm. LDA also worked well in this reaction.

Compound **103** could be utilized for subsequent reaction *in situ* at temperatures from –78°C to room temperature. Also, a pure form of compound **103** could be prepared in solution by vacuum transfer of the reaction mixture. Under certain circumstances, reactions of **103** were run using such a pure solution without the presence of lithium salt. In an attempt to isolate the pure difluoro kentene aminal, the solvent was distilled off and

the residue was distilled at reduced pressure to afford a colorless liquid. The ^{19}F NMR spectrum revealed that the distillate was the hydrolysis product N,N-dimethyl difluoroacetamide(**104**), which means that the difluoro ketene aminal is very sensitive to moisture. Indeed, quenching the reaction mixture with water gave a quantitative yield of **104**.

4.2.2 Protonation and Halogenation

Compound **103** undergoes virtually quantitative reaction with water, bromine, or iodine to give the respective N,N-dimethyl difluoroacetamide (**104**), N,N-dimethyl bromodifluoroacetamide (**105**), and N,N-dimethyl iododifluoroacetamides (**106**) in isolated yields of 92%, 89%, and 92%, respectively, based on **73a** (Figure 4-3).



103

104, X = H (92%)
105, X = Br (89%)
106, X = I (92%)

Figure 4-3. Protonation and halogenation of difluoroketne aminal.

Results have shown that protonation and halogenation occur on the β-carbon atom of difluoroketene aminal **103**, which is consistent with analogous results for the electrophilic additions of 1,1-difluoro-2, 2-diphenylthioethylene.[101a,c] Usually, electrophilic additions to a 1,1-difluoro-olefin proceed so that the intermediate has the positive charge on the carbon bearing the fluorine, where the π-donor ability of fluorine

favors this orientation for the addition. For example, in the case of electrophilic addition to $Cl_2C{=}CF_2$, the addition occurs to put the positive charge on the carbon bearing the fluorines.[136] Also, destabilization of a carbocation β to the fluorines via σ-inductive effect is a contributing factor.[136]

In our case, addition of the electrophile to the carbon bearing fluorine results in a species stabilized by α-nitrogen, but destabilized by β-fluorine as shown in figure 4-4. Addition to the nitrogen-bearing carbon would result in the carbocation stabilized by the π-donation of fluorine. Our observation that electrophiles add to $CF_2{=}C(NMe_2)_2$ at the difluoromethylene carbon, is consistent with the fact that nitrogen is much better able to stabilize a positive charge than fluorine.

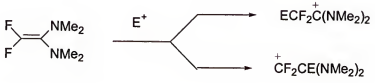
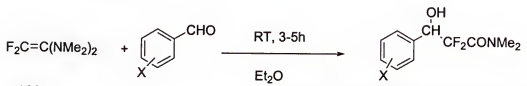


Figure 4-4. Addition of the electrophile to difluoroketene aminal.

4.2.3 Reaction with Aldehydes and Ketones

Difluoroketene aminal was found to condense with various substituted benzaldehydes at room temperature to give good yields of the respective N,N-dimethyl-2,2-difluoro-3-hydroxy-3-arylpropionamides (**107**) (Figure 4-5). However, in reactions with a number of ketones or aldehydes bearing an α-hydrogen, such as acetophenone, acetone, or butyraldehyde, no condensation or little product analogous to **107** could be observed. In each case, N,N-dimethyl difluoroacetamide (**104**) was obtained as the main

product, a result which indicated that **103** must prefer to act as a base rather than a nucleophile in such reactions. Reaction of **103** with benzophenone did not give any addition product, even with refluxing. Lewis acid catalysis, such as $TiCl_4$, BF_3, $SnCl_4$ and ZnI_2, did not help the reaction, with the Lewis acid presumably forming complex with the difluoroketene aminal rather than with carbonyl groups.



103

107a) X = H (72%), **b**)X=4-Me (79%)
c) X = 2-Br (78%), **d**) X=4-Br (80%)
e) X = 4-OMe (70%).

Figure 4-5. Reaction of difluoroketene aminal with aldehydes.

Non-fluorinated ketene aminal, CH_2=C $(NMe_2)_2$, undergo readily alkylation with alkyl halides to give amidinium salts,[138] with C-alkylation dominating due to the formation of the charge-stabilized cation. Hydrolysis of such amidinium salts under basic conditions afforded substituted amides. However, alkylation of difluoroketene aminal didn't occur at difluoromethylene position, even under refluxing conditions. Addition of benzyl bromide, allylbromide or iodomethane into difluoro ketene aminal solution in hexane formed white percipitate, which after hydrolysis gave **104**. Probably the alkylation occurs at the nitrogen site instead of the difluoromethylene site.

4.2.4 Acylation

Acylation of difluoroketene aminal with acid chlorides occurs to give difluoroketone derivatives **(108)** upon acidic workup. Addition of an acyl chloride to the

difluoroketene aminal in hexane forms a white solid, which upon workup gave low yields of the acylation product. Addition of two equivalents of triethylamine gave somewhat higher yields as shown in figure 4-6. As evidenced from this scheme, better yields are obtained with aromatic acyl chlorides, while the method has poor preparative interest when aliphatic acyl chlorides are used. The low yields for aliphatic acid chlorides are probably due to the competition of deprotonation of the acyl chloride by the reagent affording N,N-dimethyl difluoroamide as by-product. The overall relatively low yields presumably are due to the competitive nucleophilic attack of the amine nitrogen at the carbonyl group of acyl chlorides.

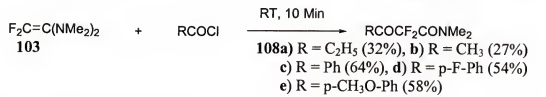


Figure 4-6. Acylation of difluoroketene aminal.

4.2.5 Synthesis of α-monofluoroalkanic amides

Compound **103** was also found to undergo a facile addition-elimination process upon addition of 1 equivalent of alkyllithium at room temperature [101b,c], with the net result that, upon hydrolytic workup, reasonable yields of the respective α-fluoroacetamides **109** were obtained (Figure 4-7). The intermediates, mono-fluoroketene aminals (**110**), could also be detected by ^{19}F NMR, but being also sensitive to moisture, are not isolated. ^{19}F NMR spectra of the reaction mixture from adding PhLi showed a peak at –146.26 ppm (triplet) for **110a** and at –158.95 ppm (singlet) for **110b** that

confirmed the formation of **110**. The difluoroketene aminal is also reactive toward Grignard reagents, but the reaction is relatively sluggish and the product yield much lower. For example, the reaction with n-butylmagnesium bromide in diethyl ether at room temperature for 3 days gave **109a** in 30% yield.

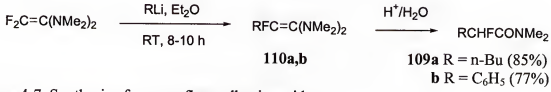


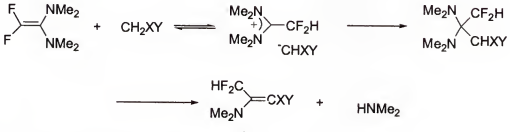
Figure 4-7. Synthesis of α-monofluoroalkanic amides.

4.2.6 Condensation Reactions of 1,1-Bis(dimethylamino)-2,2-difluoroethene with Carbon Compounds with Relatively Acidic Hydrogens

With demonstrated basicity and nucleophilicity of difluoro ketene aminals at the β-carbon atom, it seemed likely that compound **103** would react with various carbon acids. Proton transfer between the two reactants would provide the corresponding amidinium ion and carbanion; combination of the ions, followed by elimination of dimethylamine as appropriate, should then lead to the substituted enamine (**111**). These transformations are summarized in Figure 4-8.

We found that the difluoroketene aminal reacted readily with a variety of well-known carbon acids when mixed in hexane solution at room temperature. Difluoro ketene aminal **103** reacted with ethyl cyanoacetate and with nitromethane to give **111a** and **111b** as a mixture of *cis* and *trans* isomers, respectively. From difluoroketene aminal and malononitrile, diethyl malonate, **111b** and **c** were isolated. In each case these products were accompanied by N,N-dimethyl difluoroacetamide, indicating hydrolysis of **103** had

occurred as a side reaction (maybe the major reaction). This hydrolysis proved to be a common feature of these reactions.[139]



111

111a) X = CN, Y = CO_2Et (36%); **b**) X = H, Y = NO_2 (52%);
c) X, Y = CO_2Et (30%); **d**) X, Y = CN (22%).

Figure 4-8. Reactions of difluoroketene aminal with carbon compounds with relatively acidic hydrogens

In conclusion, base-catalyzed dehydrofluorination of 1,1-bis(dimethylamino)-2,2,2-trifluoroethane (**73a**) gave difluoro ketene aminal (**103**) in high yield. Alkylations of difluoro ketene aminal with various electrophiles were successful. The reactivity of difluoro ketene aminal showed both electrophilic and nucleophilic character.

4.3 Experimental

4.3.1 Protonation and Halogenation

N,N-Dimethyl difluoroacetamide, **104.**

To a solution of 1,1-bis(dimethylamino)-2,2,2-trifluoroethane (1.7g, 10mmol) in ether (5mL) at -78°C under try nitrogen was added n-butyllithium (2.5M in hexanes, 4.5mL). After that the reaction mixture was allowed to warm to room temperature and stirred for 10 hours. ^{19}F NMR spectra showed that the starting material was gone and a

new peak (-114.10ppm) occurred. Water was added slowly. 25 mL of ether was added. The solution wad washed with brine and dried ($MgSO_4$). After the solvent was removed, the residue was distillated at reduced pressure to give the product 1.14g (92%). bp 64-65 ^{o}C/ 30 mmHg; ^{1}H NMR δ 2.30 (t, 3H, J=1.5 Hz), 2.41 (t, 3H, J=1.0 Hz), 5.77 (t, 1H, J=53.7 Hz); ^{19}F NMR δ -122.72 (d, 2F, J=53.7 Hz); ^{13}C NMR δ 35.7, 109.6 (t, J=249.8 Hz), 161.8 (t, J=24.7 Hz); IR (neat): 2948.6, 1679.5, 1513.7, 1408.7, 1371.9, 1259.9, 1107.9, 1059.6, 863.6, 725.2; HRMS Calcd for $C_4H_7F_2NO$: 124.0574; Found 124.0564.

N,N-dimethyl bromodifluoroacetamide, **105**. Procedure is same as above. Yield 89%; bp 71-72 ^{o}C/ 8 Torr; ^{1}H NMR δ 2.28 (t, 3H, J=1.7 Hz), 2.31 (s, 3H). ^{19}F NMR δ -53.96 (s, 2F). ^{13}C NMR δ 36.86, 37.10, 111.59 (t, J=314.3 Hz), 158.97 (t, J=26.2 Hz). IR (neat): 2931.7, 1678.3, 1495.2, 1402.7, 1260.2, 1198.6, 1090.6, 942.4, 847.8, 714.2 cm^{-1}. HRMS (EI) Calcd for $C_4H_6BrF_2NO$ 200.9601; Found 200.9600.

N,N-dimethyl iododifluoroacetamide, **106**. Procedure is same as above. Yield 92%; bp 89-90 ^{o}C/ 6 Torr; ^{1}H NMR δ 3.02 (s, 3H), 3.12 (t, 3H, J=1.7 Hz); ^{19}F NMR δ -51.03 (s, 2F); ^{13}C NMR δ 37.6, 38.5, 90.2 (t, J=321.8 Hz), 159.9 (t, J=26.0 Hz); IR (neat): 2931.7, 1677.1, 1495.1, 1400.7, 1259.1, 1198.5, 1090.6, 942.3, 847.9, 713.1. HRMS Calcd for $C_4H_6F_2INO$ 248.9462; Found 248.9461.Anal. Cacld for $C_4H_6F_2INO$: C, 19.28; H, 2.41; N, 5.62; Found C, 19.74; H, 2.58; N, 5.70.

4.3.2 General Procedure for the Preparation of 2,2-difluoro-3-hydroxy-3-phenylpropionamides

A n-BuLi solution in the hexane (2.5 M in hexanes) was added dropwise to a stirred solution of 1,1-bis(dimethylamino)-2,2,2-trifluoroethane in dry ether at -78 oC. Then the reaction mixture was allowed to warm up to room temperature and stirred 10 hours. The aldhyde solution in dry ether was added and stirred 3-5 hours. The reaction was quenched with 5% HCl solution and extracted with ether. The combined organic layer was washed with brine, dried over $MgSO_4$, and filtered. The solvent was removed under reduced pressure, and the crude product was purified by distillation or flash chromatography.

N,N-dimethyl 2,2-difluoro-3-hydroxy-3-phenyl propionamide, **107a**. Yield 72%; bp 120-122 °C/ 5 Torr; ^{1}H NMR δ 3.04 (t, 3H, J=1.2 Hz), 3.14 (t, 3H, J=2.2 Hz), 5.27 (dd, 1H, J=21.5, 3.4 Hz), 4.37 (s, 1H), 7.28-7.58 (m, 5 H); ^{19}F NMR δ -104.66 (d, 1F, J=293.0 Hz), -118.74 (dd, 1F, J=29.5 Hz); ^{13}C NMR δ 36.6, 73.3 (ddd, J=29.7, 23.7, 7.7 Hz), 114.9 (dd, J=266.9, 257.8 Hz), 127.8, 128.1, 128.4, 134.7, 163.7 (t, J=28.7 Hz); IR 2939.4, 1650.0, 1497.5, 1453.0, 1408.6, 1186.2, 1090.9, 1052.7, 913.0, 735.0, 696.9; HRMS Calcd for $C_{11}H_{14}F_2NO_2$ 230.0993; Found 230.0993.

N,N-dimethyl 2,2-difluoro-3-hydroxy-3-(4-methyl)phenyl propionamide, **107b**. Yield 79%; mp 97-98 °C; ^{1}H NMR δ 2.35 (s, 3H), 3.02 (t, 3H, J=1.2 Hz), 3.12 (t, 3H, J=2.4 Hz), 4.36 (s, 1H), 5.20 (dd, 1H, J=18.6, 2.7 Hz), 7.18 (d, 2H, J=8.0 Hz), 7.36 (d, 2H, J=8.0 Hz); ^{19}F-NMR δ -104.6 (d, 1F, J=293.0 Hz), -118.9 (dd, 1F, J=293.0, 22.0 Hz);

^{13}C NMR δ 21.1, 36.7, 73.4 (ddd, J=28.7, 23.7, 7.6 Hz), 114.8 (dd, J=266.9, 258.4 Hz), 128.1, 128.6, 131.6, 138.3, 163.9 (t, J=28.0 Hz); IR 2946.4, 1654.6, 1517.6, 1406.0, 1322.4, 1185.2, 1086.6, 1048.8, 911.8, 786.1, 728.3; HRMS Calcd for $C_{12}H_{15}F_2NO_2$ 244.1149; Found 244.1160. Anal. Calcd for $C_{12}H_{15}F_2NO_2$: C, 59.26; H, 6.17; N, 5.76. Found: C, 59.27; H, 6.25; N, 5.66.

N,N-dimethyl 2,2-difluoro-3-hydroxy-3-(2-bromo)phenyl propionamide, **107c**. Yield 77%; mp 103-104 °C; ^{1}H NMR δ 2.30 (t, 3H, J=1.2 Hz), 2.36 (t, 3H, J=2.2 Hz), 4.65 (s, 1H). 6.23 (d, 1H, J=22.5 Hz), 6.69 (m, 1H), 7.01 (m, 1H), 7.33 (dd, 1H, J=8.1, 1.2 Hz), 8.01 (dt, 1H, J=7.8, 2.0 Hz); ^{19}F NMR δ -103.4 (d, 1F, J=293.0 Hz), -119.2 (dd, 1F, J=293.0, 22.0 Hz); ^{13}C NMR δ 36.0, 72.4 (dd, J=29.7, 23.4 Hz), 116.0 (dd, J=266.4, 257.8 Hz), 126.0, 127.5, 130.3, 131.5, 132.7, 135.5, 163.9 (t, J=28.4 Hz); IR 2946.2, 1655.1, 1475.9, 1438.4, 1406.7, 1306.8, 1184.2, 1090.6, 1049.9, 911.8, 741.9; HRMS Calcd for $C_{11}H_{12}BrF_2NO_2$ 308.0098, Found 308.0079.

N,N-dimethyl 2,2-difluoro-3-hydroxy-3-(4-bromo)phenyl propionamide, **107d**. Yield 80%; ^{1}H NMR δ 3.03 (s, 3H), 3.14 (t, 3H, J=2.0 Hz), 4.37 (d, 1H, J=3.4 Hz), 5.22 (dd, 1H, J=21.1, 3.2 Hz), 7.28 (d, 2H, J=8.5 Hz), 7.37 (d, 2H, J=8.5 Hz); ^{19}F NMR δ -104.7 (d, 1F, J=293.0 Hz), -118.8 (dd, 1F, J=293.0, 19.5 Hz); ^{13}C NMR δ 36.7, 73.1 (t, J=98.4 Hz), 114.5 (dd, J=266.4, 257.4 Hz), 122.8, 129.9, 131.1, 133.6, 163.7 (t, J=28.4 Hz); IR (neat) 2939.1, 1655.0, 1480.5, 1399.0, 1172.1, 1092.3, 1053.4, 805.6, 770.7, 677.6; HRMS Calcd for $C_{11}H_{12}BrF_2NO_2$: 308.0098, Found 308.0101; Anal. Calcd for $C_{11}H_{12}BrF_2NO_2$: C, 42.86; H, 3.90; N, 4.55. Found: C 42.87; H, 3.83; N, 4.49.

N,N-dimethyl 2,2-difluoro-3-hydroxy-3-(4-methoxy)phenyl propionamide, 107e. Yield 70%; mp 117-118°C; ^{1}H-NMR δ 3.03 (t, 3H, J=1.0 Hz), 3.14 (t, 3H, J=2.2 Hz), 3.82 (s, 3H), 4.25 (d, 1H, J=3.0 Hz), 5.21 (dt, 1H, J=21.5, 3.4 Hz), 6.92 (d, 2H, J=8.3 Hz), 7.41 (d, 2H, J=8.3 Hz); ^{19}F NMR δ -104.9 (d, 1F, J=285.6 Hz), -118.1 (dd, 1F, J=285.6, 22.0 Hz); ^{13}C NMR δ 36.7, 55.2, 73.3 (t, J=90.3 Hz), 113.4, 114.8 (dd, J=266.4, 257.4 Hz), 126.6, 129.5, 159.8, 164.0 (t, J=28.7 Hz); HRMS Calcd for $C_{12}H_{15}F_2NO_3$ 259.1020, Found 259.1023. IR: 2939.9, 1654.7, 1516.2, 1464.3, 1405.9, 1252.7, 1176.0, 1086.0, 1048.0, 911.7, 794.5, 741.8; Anal. Calcd for $C_{12}H_{15}F_2NO_3$: C,55.60; H, 5.79; N, 5.40, Found C, 55.43; H, 5.81; N, 5.34.

4.3.3 General Procedure for the Reaction Difluoro Ketene Aminal with Acid Chloride

Difluoroketene aminal (10mmol) solution in hexane was prepared as above. Acid chloride (10mmol) and triethylamine (3mL) was added to the flask containing difluoroketene aminal solution at 0°C. The reaction mixture was stirred for 10 minutes. Methylene chloride (20mL) was added, and washed with brine (10mL X 2). After distillation of the solvent, the residue was distilled or column chlomatography to get final products. The Yield are reported with respect to the difluoroketene aminal.

N,N-dimethyl 2,2-difluoro-3-oxopentanoamide, **108a**. Yield 52%; ^{1}H NMR δ 1.15 (t, 3H, J=7.1 Hz), 3.00 (t, 3H, J=.7 Hz), 3.15 (t, 3H, J=1.7 Hz), 2.72 (q, 2H, J=7.1 Hz); ^{19}F NMR δ -110.02 (s, 2F); ^{13}C NMR δ 6.71, 30.60, 36.30 (m), 110.67 (t, J=267.9 Hz), 161.27 (t, J=27.2 Hz), 198.17 (t, J=26.7 Hz); IR 2945.3, 1756.4, 1670.4, 1504.3, 1461.9,

1408.0, 1382.5, 1264.1, 1207.9, 1113.7, 1071.7, 1014.7, 956.9, 866.7, 792.5, 752.3; HRMS Calcd for $C_7H_{11}F_2NO_2$: 179.0758; Found 179.0740. Anal. Calcd for $C_7H_{11}F_2NO_2$: C, 46.93; H, 6.15; N, 7.82. Found C, 46.50; H, 6.17; N, 7.48.

N,N-dimethyl 2,2-difluoro-3-oxobutanoamide, **108b**. Yield 27%. ^{1}H NMR δ 2.37 (t, 3H, J=1.7 Hz), 3.15 (t, 3H, J=1.95 Hz), 3.00 (t, 3H, J=0.7 Hz). ^{19}F NMR δ -110.07 (s, 2F). ^{13}C NMR δ 24.93, 36.43, 110.54 (t, J=267.9 Hz), 161.27 (t, J=28.1 Hz), 194.98 (t, J=25.4 Hz). IR (neat): 2947.7, 1758.7, 1665.6, 1513.2, 1461.8, 1408.5, 1362.9, 1253.7, 1211.5, 1106.1, 1049.0, 996.5, 965.4, 862.3, 753.3. HRMS (CI) Cacld for $C_6H_{10}F_2NO_2$ (M+1) : 166.0680; Found 166.0676. Anal. Cacld for $C_6H_9F_2NO_2$: C, 43.64; H, 5.45; N, 8.48; Found C, 42.24; H, 5.44; N, 7.85.

N,N-dimethyl 2,2-difluoro-3-oxo-3-phenylpropanoamide, **108c**. Yield 64%. ^{1}H NMR δ 3.13 (s, 3H), 3.24 (t, 3H, J=1.4 Hz), 7.47 (m, 2H), 6.63 (m, 1H), 8.09 (m, 2H). ^{19}F NMR δ -103.26 (s, 2F). ^{13}C NMR δ 36.79 (m), 111.56 (t, J=264.4 Hz), 128.41, 128.70, 130.11, 133.70, 134.63, 161.54 (t, J=27.2 Hz). IR 2945.3, 1711.5, 1668.3, 1598.8, 1499.9, 1450.5, 1407.0, 1286.0, 1257.3, 1156.5, 1107.7, 1061.8, 941.5, 861.7, 717.5. HRMS Cacld for $C_{11}H_{12}F_2NO_2$: 228.0836; Found 228.0841. Anal. Calcd for C11H12F2NO2

N,N-dimethyl 2,2-difluoro-3-oxo-3-(4-fluoro-phenyl)propanoamide, **108d**. Yield 54%. ^{1}H NMR δ 3.00 (s, 3H), 3.13 (s, 3H), 7.13 (t, J= 8.6 Hz, 2H), 8.09 (dd, J=8.1, 5.3 Hz, 2H). ^{19}F NMR δ -102.01 (m, 1F), -103.22 (s, 2F). ^{13}C NMR δ 36.45, 111.40 (t, J=264.54 Hz), 115.84 (d, J=21.8 Hz), 128.02, 132.83 (d, J=9.2 Hz), 161.18 (t, J=26.3 Hz), 164.60,

168.01, 184.89 (t, J=27.5 Hz). IR: 2943.6, 1707.9, 1666.8, 1602.1, 1508.1, 1414.1, 1278.9, 1237.8, 1149.7, 1108.5, 1061.5, 938.1, 867.6, 844.1. HRMS (EI) Calcd. for $C_{11}H_{10}NF_3O_2$: 245.0664, Found: 245.0619.

N,N-dimethyl 2,2-difluoro-3-oxo-3-(4-methoxy-phenyl)propanoamide, **108e**. Yield 58%. ^{1}H NMR δ 2.87 (s, 3H), 2.96 (s, 3H), 3.71(s, 3H), 6.81 (d, 2H, J=8.8 Hz), 7.93 (d, 2H, J=8.8 Hz). ^{19}F NMR δ -102.75 (s) ppm; ^{13}C NMR δ 36.22, 36.30, 55.15, 111.37 (t, J=263.4 Hz), 113.76, 123.97, 132.23, 161.20 (t, J=26.4 Hz), 164.52, 184.37 (t, J=26.3 Hz); IR: 2943.6, 1708.2, 1668.4, 1598.1, 1574.2, 1513.9, 1460.9, 1425.6, 1406.3, 1321.9, 1264.1, 1182.6, 1154.7, 1061.3, 1026.2, 9393.9, 889.8, 869.4, 845.4; HRMS (EI) Calcd. for $C_{12}H_{13}NF_2O_3$: 257.0863, found: 257.0866.

4.3.4 Reaction with excess of n-butyllithium

N,N-dimethyl 2-fluorohexanonamide, **109a**. To a solution of 1,1-bis(dimethylamino)-trifluoroethane (1.7g, 10mmol) in ether (5mL) at -78°C under try nitrogen was added n-butyllithium (2.5M in hexanes, 4.5mL). After that the reaction mixture was allowed to warm to room temperature and stirred for 10 hours. ^{19}F NMR spectra showed that the starting material was gone and a new peak (-114.1ppm) occurred. 6 mL of n-butyllithium (2.5 M in hexanes) was added slowly. The reaction mixture was stirred at room temperature for 8 hours. 50 mL of ether was added. The solution wad washed with water and dried ($MgSO_4$). After the solvent was removed, the residue was distillated at reduced pressure to give the product 1.37g (85%). B.p. 90-92 °C/ 6 Torr. ^{1}H NMR δ 0.86 (t, 3H,

J=6.9 Hz), 1.26-1.83 (m, 6H), 2.87 (d, 3H, J=1.0 Hz), 2.97 (d, 3H, J=1.7 Hz), 5.00 (ddd, 1H, J=49.3, 8.6, 4.4 Hz). ^{19}F NMR δ -186.03 (ddd, 1F, J=51.2, 32.2, 2.2 Hz). ^{13}C-NMR δ 13.6, 22.1, 26.7 (d, J=3.5 Hz), 31.5 (d, J=21.1 Hz), 35.73 (m), 36.43 (m), 89.6 (d, J=178.8 Hz), 168.7 (d, J=21.1 Hz). IR (neat): 2958.4, 1659.8, 1503.3, 1467.6, 1419.8, 1380.0, 1354.4, 1261.8, 1166.0, 1120.8, 1015.8, 889.1, 781.8, 717.5cm^{-1}. HRMS Calcd for $C_8H_{16}FNO$ 162.1294; Found 162.1308.

N,N-dimethyl 2-fluoro-2-phenylacetamide, **109b**. mp 56-58°C. ^{1}H NMR δ 2.19 (s, 3H), 2.52 (s, 3H), 5.88 (d, 1H, J=49.1 Hz), 7.00-7.12 (m, 3H), 7.39-7.45 (m,2H). ^{19}F NMR δ -173.23 (d, 1F, J=49.1 Hz). ^{13}C NMR δ 35.8, 36.2, 90.0 (d, J=178.8 Hz), 126.8, 128.7, 129.3, 134.1 (d, J=19.6 Hz), 167.5 (d, J=22.7 Hz). IR (KBr): 2941.1, 1663.3, 1497.9, 1456.0, 1404.4, 1258.9, 1193.6, 1149.7, 1040.6, 912.3, 741.5, 650.2, 698.1. HRMS Calcad for $C_{10}H_{12}FNO$ 181.0903; Found 181.0910. Anal. Calcd for $C_{10}H_{12}FNO$: C, 66.30; H, 6.63; N, 7.73. Found C, 66.19; H, 6.36; N, 7.71.

4.3.5 General Procedure for the Condensation Reactions of Difluoroketene Aminal with Carbon Compounds with Relatively Acidic Hydrogens

Difluoroketene aminal (10mmol) solution in hexane was prepared as above. Appropriate carbon acids (8mmol) was added to the flask containing difluoroketene aminal solution at room temperature. The reaction mixture was stirred for 10 minutes. After distillation of the solvent, the residue was distilled or column chromatography to get final products. The Yields are reported with respect to the carbon acids.

2-Cyano-3-dimethylamino-4,4-difluoro-but-2-enoic acid ethyl ester, **111a**.

Yield 36%; bp: 145-147°C/1 Torr. Reaction gave a mixture of *cis* and *trans* products and the ratio is 100:23.

The major compound: ^{1}H NMR 1.25 (t, J=6.9 Hz, 3H), 3.31 (s, 6H), 4.16 (q, J=6.9 Hz, 2H), 7.59 (t, J=52.5 Hz, 1H); ^{19}F NMR -117.29 (d, J=50.9 Hz); ^{13}C NMR 13.93, 44.22, 61.15, 75.76, 108.32 (t, J=243.9 Hz), 117.13, 161.76 (t, J= 21.8 Hz), 165.02.

The minor compound: ^{1}H NMR 1.25 (t, J=6.9 Hz), 3.11 (s, 6H), 4.16 (q, J=6.9 Hz, 2H), 6.52 (t, J=51.9 Hz, 1H); ^{19}F NMR -120.90 (d, J=50.9 Hz); ^{13}C NMR 13.93, 44.22, 60.99, 75.76, 111.25 (t, J= 247.4 Hz), 117.35, 158.34 (t, J=20.6 Hz), 162.32.

IR: 2206.8, 1746.6, 1691.7, 1582.0. HRMS (EI) Calcd for $C_9H_{12}O_2N_2F_2$: 218.0867; Found: 218.0900. Element Anal. Calcd. For $C_9H_{12}O_2N_2F_2$: C 49.54, N 12.84, H 5.50; Found: C 49.46, N 13.04, H 5.89.

(1-Difluoromethyl-2-nitro-vinyl)-dimethylamine, **111b**. Yellow solid was separated by column chromatography (7:3 of ethyl acetate: hexane) Yield: 52%. Reaction gave a mixture of cic and trans products and the ratio is 30:1.

The major compound: ^{1}H NMR 3.13 (s, 6H), 6.60 (s, 1H), 7.94 (t, J=52.5 Hz, 1H). ^{19}F NMR -121.82 ppm (d, J=53.3 Hz).

The minor compound: ^{1}H NMR 3.13 (s, 6H), 6.64 (s, 1H), 5.99 (t, J=52.8 Hz, 1H); ^{19}F NMR -117.27 (d, J=50.9 Hz). ^{13}C NMR 42.09, 107.59 (t, J=244.3 Hz), 116.18, 150.23 (t, J=21.7 Hz); HRMS Calcd. for $C_5H_8O_2N_2F_2$ 116.0554; found 166.0582; Element anal. For $C_5H_8O_2N_2F_2$ Calcd. C: 36.14, H 4.82, N 16.86; found C 36.06, H 4.75, N 16.43.

Diethyl 2-(1-dimethylamino-2,2-difluoro-propylidene-malonate, **111c**.

Yield: 30%; ^{1}H NMR 1.24 (t, J=7.2 Hz, 6H), 3.01 (s, 6H), 4.16 (q, J=7.2 Hz, 4H), 7.01 (t, J=53.3 Hz, 1H); ^{19}F NMR -118.14 (d, J=53.3 Hz, 2F); ^{13}C NMR 14.01, 43.02 (t, J=3.0 Hz), 60.70, 99.49 (t, J=6.3 Hz), 110.83 (t, J=244.3 Hz), 155.52 (t, J=20.7 Hz), 166.57; HRMS (EI): Calcd. for $C_{11}H_{17}F_2NO_4$: 265.1126; Found: 265.1139.

2-(1-Dimethylamino-2,2-difluoro-propylidene)-malononitrile, **111d**.

The reaction was completed in 1 hour. Yellow solid was isolated by column chromatography (7:3 of ethyl acetate: hexane). Yield 22%; ^{1}H NMR 3.39 (s, 6H), 6.70 (t, J=51.4 Hz, 1H); ^{19}F NMR -117.92 (d, J=51.4 Hz, 2F); ^{13}C NMR 43.62, 110.22 (t, J=248.3 Hz), 114.16, 114.32, 158.59 (t, J=22.2 Hz); HRMS (EI) Calcd for $C_7H_7N_3F_2$: 171.0608; Found: 171.0643.

CHAPTER 5
CYCLOADDITION REACTIONS OF 1,1-BIS(DIMETHYLAMINO)-2,2-DIFLUOROETHENE

5.1 Diverse Cycloadditon Chemistry Leading to Overall Michael Addition in the Reaction of 1,1-Bis(dimethylamino)-2,2-difluoroethene with α,β-Unsaturated Aldehydes, Ketones, Esters, and Nitriles

Conjugate additions of difluoro enolate species to potential α,β-unsaturated Michael substrates are uncommon. There are only few reports related to this topic. Taguchi's group provides some examples of Michael addition of 2,2-difluoroketene silyl acetals, and these workers also describe some of the limitations of using difluoro enol ethers and ketene acetals for this purpose[86-87,94] (Figure 5-1). Similarly, difluoroenoxysilanes, which prepared from the condensation of trifluoromethyltrimethylsilane with non fluorinated acylsilanes under catalytic fluoride activetion, undergo 1,4-additions with enones to give 2,2-difluoro-1,5-diketones.[93] Similar to the reaction of difluoroenolether and difluoroenolates, 1,2-addition occurred with α,β-unsaturated aldehydes.

In contrast to the limited Michael reactivity exhibited by difluoro enol ethers and ketene acetals, difluoro Reformatsky reagents give exclusively aldol-type products in the few reported examples of their reaction with α,β-unsaturated aldehydes or ketones[91] (Figure 5-2) as summarized in more detail in chapter 1.2.

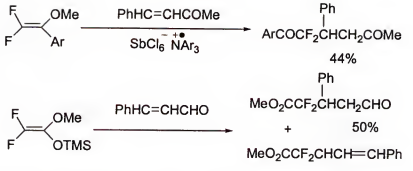


Figure 5-1. Michael addition in the reaction difluoro enolates with α,β-unsaturated aldehydes, ketones.

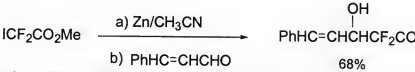


Figure 5-2. 1,2-Addition of difluoro enolate with α,β-unsaturated aldehyde.

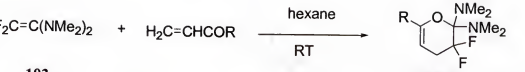
In general, enamines and ketene aminals are much more reactive than enol ethers and ketene acetals in their reactions with α,β-unsaturated aldehydes, ketones, esters, and nitriles, and a diversity of chemistry has been reported for such reagents including Michael additions, [2+2] cycloadditions and, hetero-Diels-Alder reactions.[140-148] A recent report describes Michael additions of mono-fluorinated enamines derived from α-fluoroacetophenones and pyrrolidine.[149] It was expected that difluoro ketene aminals would be considerably more reactive towards such α,β-unsaturated Michael substrates than the other difluoro enolate-type reagents which have been studied. Recognizing that discovery of a reagent which would participate in overall Michael addition of a difluoro enolate-type building block would be a useful synthetic accomplishment, we initiated an investigation of the reactions between difluoroketene aminal and acrolein, methyl vinyl ketone, methyl acrylate, acrylnitrile, methyl methacrylate, and methacrylonitile.

5.1.1 Results and Discussion

5.1.1.1 Cycloadditions

Difluoro ketene aminal indeed proved to be very reactive toward all of these substrates, with the reactions being complete after 5 minutes at room temperature, except for those with methyl methacrylate and methacrylonitrile which required 10 minutes at 90 °C to reach completion. Reactions of **103** with acrolein and methyl vinyl ketone led cleanly to hetero-Diels-Alder products **112** (Figure 5-3), whereas those with the ester and nitrile substrates led exclusively to [2+2] adducts **113** and **114**, respectively (Figure 5-4).

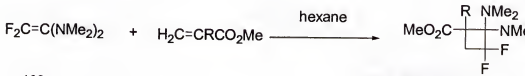
Competition between [2+2] and [2+4] processes was unable to be observed in any of these reactions. In order to intercept a potential [2+2] "intermediate" in the hetero-Diels-Alder reaction of **103** with acrolein, the reaction was carried out at –78 °C. Indeed, reaction did occur, although very slowly, but the only product which was observable, following the reaction by ^{19}F NMR, was the [2+4] adduct **112a**. Conversely, it was not possible to observe rearrangement of [2+2] adduct **113a** to a [4+2] adduct by heating its reaction mixture up to a temperature which led to decomposition. The [2+2] adducts are readily distinguishable from the [2+4] adducts because the fluorine NMR signals for the former compounds are all AB multiplets, whereas those of the latter compounds are all single multiplets. Thus the nature of the products was always clearly discernible by NMR analysis of the crude product mixtures.



103

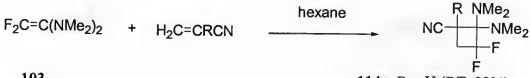
112a, R = H (70%)
112b, R = Me (72%)

Figure 5-3. [4+2] Cycloaddition of difluoroketene aminal.



103

113a, R = H (RT, 87%)
113b, R = Me (90°C, 84%)



103

114a, R = H (RT, 83%)
114b, R = Me (90°C, 46%)

Figure 5-4. [2+2] Cycloadditions of difluoroketene aminal.

The dihydropyrans obtained from the hetero-Diels-Alder reaction and the cyclobutane products obtained from the [2+2] reaction were readily isolated and characterized, although they are quite sensitive to moisture. These reactive compounds themselves could well be useful fluorinated building blocks. One such example will be discussed later.

In all likelihood, the two cycloaddition processes did not involve a common mechanistic pathway. Rather in those cases where a Diels-Alder reaction is observed, the reaction probably involves a concerted pericyclic process, as has been proposed by other workers who have studied the Diels-Alder reactions of acrolein with electron-rich alkenes.[140-141,148] The reactions of **103** with acrolein (and with methyl vinyl ketone) are

ideally matched for a reverse electron-demand Diels-Alder (LUMOdiene-controlled) reaction. There can be no doubt that **103** will have an exceptionally high HOMO, whereas acrolein and methyl vinyl ketone will have low LUMOs (relative to butadiene).[150]

In contrast, methyl acrylate and acrylonitrile, which should have higher LUMO energies than the aldehyde and ketone, are known to preferentially form [2+2] adducts in their reactions with nonfluorinated ketene acetals. Therefore, it should have been no surprise that cyclobutane products were obtained with each of the esters and nitriles, presumably via a two-step process involving zwitterionoic intermediates.

5.1.1.2 Hydrolysis to Michael products

All of the adducts could be hydrolyzed, under carefully controlled conditions, to produce the respective Michael addition products **115-117**. Theses hydrolyses are carried out in methylene chloride, using a limited amount of 3% HCl, at room temperature (Figure 5-5).

5.1.2 Conclusions

Difluoro ketene aminal **103** is a highly nucleophilic *in situ* reagent which undergoes clean [2+4] cycloadditions with α,β-unsaturated aldehydes and ketones and clean [2+2] cycloadditions with α,β-unsaturated esters and nitriles. Both types of adducts proved to be readily converted, by mild hydrolysis, to the overall Michael addition

products. This sequence of two reactions presently comprises the only reported generally useful method for reliably obtaining Michael addition products, to the exclusion of 1,2-adducts, from a difluoro enolate-type reagent.

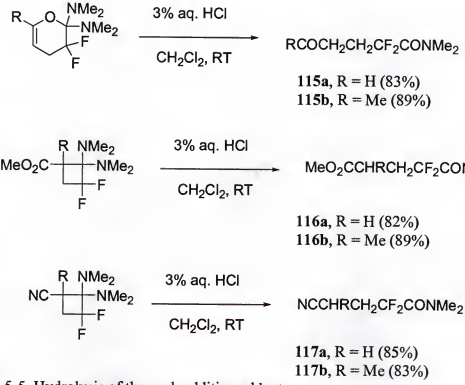


Figure 5-5. Hydrolysis of the cycloaddition adducts.

5.2 Synthesis of Monofluoro-Aminopyridine

The pyridine nucleus is a major component of a variety of natural products and drugs.[151] Due to its unique position in medicinal chemistry and the pharmacological importance of functionalized pyridines, many synthetic pathways for pyridines have been developed.[152] Fluorinated pyridines have also been exploited as synthons for numerous transformations to give valuable heterocyclic compounds.[153] Fluoropyridines have also been used as crop protection chemicals, pharmaceuticals and biochemical reagent.[154]

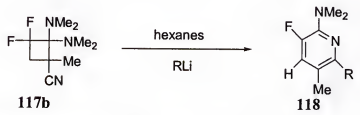
Exchange-fluorination of halopyridines or diazotization of aminopyridines represent the main routes to fluoropyridine compounds.[155,156] Direct fluorination or reaction of modern fluorinating agents with the pyridine ring has been recently attempted,[157] but harsh reaction conditions and/or risk of explosion of the reagents caused problems. Fluorinated building blocks offer a nice alternative for making these kinds of compounds. Nucleophilic addition to a cyano group followed by ring closure is a well-documented approach to different heterocycles.[158] Nucleophilic addition to the cyano group of a cyano substituted cyclobutane to undergo cyclization via ring opening and intramolecular attack at a remote electrophilic site has been little explored.

With the compound **117b** in hand, this compound was considered to be a good model for trying this kind of reaction. Reaction of compound **117b** with alkyllithium lithiation reagents gave aminopyridine derivatives **118**. Details of this reaction and its scope are discussed below.

5.2.1 Results and Discussion

Treatment of **117b** in hexane at 0°C with 1 equivalent of phenyl lithium in hexane led to formation of a yellow product mixture, which was quenched with H_2O after stirring at room temperature for an additional 5 hours. The starting material was not detected by ^{19}F NMR, and a set of doublet peaks and broadened peaks were detected at -136ppm and –180 ppm. Flash chromatography on silica gel allowed isolation of the pure aminopyridine derivative **118c** in 46% yield (Figure 5-6). Similar results were obtained following exposure of **117b** to BuLi, MeLi and t-BuLi leading to isolation of

aminopyridine products **118** in generally low yields. The low isolated yield of **118d** is attributed to the production of non-isolated side products arising in the reaction.



117b **118**

Figure 5-6. Synthesis of monofluoro-aminopyridine.

A limited number of experiments were carried out to further define the reaction scope. Organomagnesium reagents do not appear to be sufficiently reactive to take part in the reaction based on the lack of reaction of EtMgBr (0°C to RT/THF) with **117b**, and refluxing the reaction mixture gave a mess. The related 2,2-bis(dimethylamino)-3,3-difluoro-cyclobutanecarbonitrile was used in reactions with lithium reagents under various reaction conditions (RT and refluxing) but it failed to give any pyridine products.

Table 5-1. Reaction of **117b** with alkyllithium

Product	RLi	Condition	Time	yield (%)
118a	MeLi/ether	0°C to RT	2.5 h	81
118b	BuLi/hexane	0°C to RT	2 h	42
118c	PhLi	0°C to RT	3h	46
118d	t-BuLi/hexane	0°C to RT	overnight	24

The structures of the 3-fluoro-2-pyridineamines **118** weredetermained by their ^{1}H, ^{13}C and ^{19}F NMR spectral characteristics and confirmed by HRMS and/or elementary

analysis. All of the fluorine NMR spectra showed doublets at –133 to -137 ppm with coupling constants around 14 Hz, which were identical to the coupling constants of the signals at 6.9 ppm in the respective proton NMR spectra.

Figure 5-7 shows a plausible mechanism for the formation of 3-fluoro-2-pyridineamine **118**. As mentioned above, a broad peak was observed in the reaction mixture at -180 ppm, which is where the fluoride ion signals should occur.

In summary, we found a new, but limited method for the synthesis of monofluorinated aminopyridines **118** by the reaction of 2,2-bis(dimethylamino)-3,3-difluoro-1-methylcyclobutanecarbonitrile **117b** with organic lithium reagents in moderate to good yields.

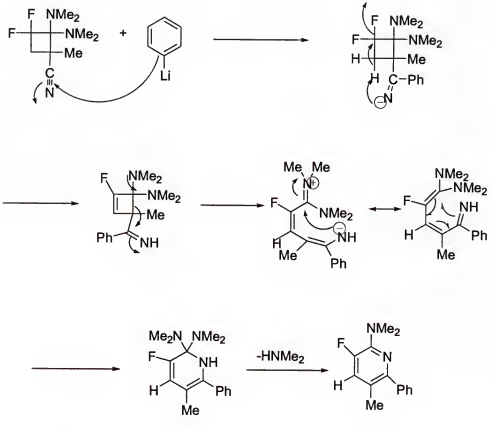
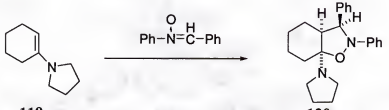


Figure 5-7. Proposed mechanism of the formation of monofluoro-aminopyridine.

5.3 1,3-Dipolar Cycloadditions

1,3-Dipolar cycloaddition reactions are one of the most useful methods for the synthesis of five-membered hetrocyclic compounds.[159] In particular, isoxazolidines which are obtained by the reaction of nitrones with olefins, can be converted into γ-aminoalcohols as precursors for biologically active compounds such as alkaloids and β-lactam antibiotics.[160]

Regio- and stereo-specific 1,3-cycloaddition reactions of nitrones to enamines are known to give 5-aminoisoxazolidine derivatives,[161] as for instance in the reaction of pyrrolidinocyclohexene (**119**) with α-N-diphenyl nitrone, which affords compound (**120**) (Figure 5-8).[162] In connection with our cycloaddition studies, we have investigated the reaction of difluoro ketene aminal **103** with nitrones.



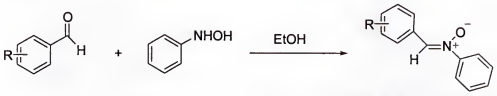
119 **120**

Figure 5-8. 1,3-Dipolar cycloaddition of enamine with α-N-diphenyl nitrone.

5.3.1 Results and Discussion

Phenylhydroxyamine is made by zinc dust and ammonium chloride reduction of nitrobenzene.[163] N-Phenylnitrones **121a-d** were prepared in excellent yield (85-92%) by mixing equimolar amounts of phenylhydroxyamine and the appropriate substituted

benzaldehyde in a minimum quantity of alcohol, and allowing the mixtures to stand at room temperature for two hours[164] (Figure 5-9).



121a, R = H (92%); **b**, R = p-F (88%)
c, R = p-MeO (86%); **d**,R = 2-Me (85%)

Figure 5-9. Preparation of α-N-phenyl nitrone

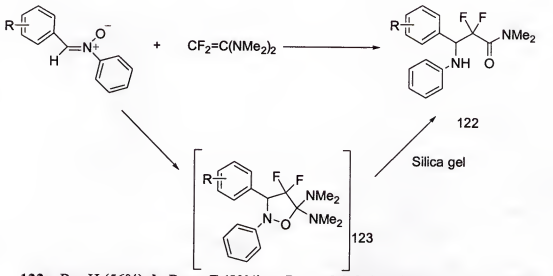
The reactions of nitrones **121a-d**, in DMF at 70°C, with a hexane solution of difluoro ketene aminal **103**, directly gave the ring-opened products **122a-d** upon workup (Figure 5-10). Presumably the reaction proceeded via formation of initial cycloaddition intermediates, such as **123**, which can be detected in the crude product mixture (^{19}F NMR at –120 ppm). Conversion of **123** to **122** occurs during silica gel flash chromatography. The reaction time was much longer than the earlier discussed [2+2] and [2+4] cycloaddition reactions.

The structures of **122a-d** were assigned on the basis of their NMR spectra, mass spectra and they were confirmed by elemental analysis (for compound **122a**). In the ^{19}F NMR spectra of **122a-d** the two fluorine signals appear as a well-separated AB system (i.e., δ -102.11 and –105.83 for **122a**). The signal for the single methine group in the ^{1}H spectra was observed as a triplet at about 5.14 ppm.

In order to extend the reaction scope, N-methyl α-phenylnitrone and N-benzyl α-phenylnitrone was synthesized. The reaction of N-methyl α-phenylnitrone and N-benzyl

α-phenylnitrone with difluoro ketene aminal at same reaction condition was performed, however the only product observed was N,N-dimethyl difluoroamide. Presumably, difluoro ketene aminal **103** acts as a base and abtracts the proton of the methyl or methylene group in these nitrones, which is consistent with the earlier discussed reaction of difluoro ketene aminal with ketones and aldehydes.

In conclusion, difluoro ketene aminal **103** undergoes 1,3-dipolar cycloadditions with N-phenylnitrones. The cycloaddition adducts were readily converted to 2,2-difluoro-3-phenylamino-propionamides in moderate yield.



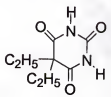
122a, R = H (56%); **b**, R = p-F (50%); **c**, R = p-MeO (52%); **d**,R = 2-Me (38%)

Figure 5-10. 1,3-Dipolar cycloaddition of difluoroketene aminal with α-N-diphenyl nitrone.

5.4 Synthesis of Novel Fluorinated Derivatives of 1,3-Dimethylbarbituric Acid

Barbiturates, such as barbital **124**, which are substituted derivatives of barbituric acid, were the first synthetic drugs found to exert significant action on the central nervous

system.[165] They also show biological convulsant, anticonvulsant and analeptic effects. Such pharmacological properties of barbiturates have been reviewed.[166] Recently, it was found that derivatives of 5-benzylbarbituric acid are potent chemotherapy agents useful in the treatment of both cancer and AIDS.[167-168]

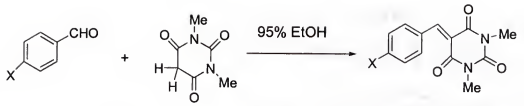


124

It is also well recognized that the selective introduction of fluorine substituents into a biologically active compound can enhance its pharmacological properties or increase its therapeutic effectiveness.[8a,169,170] Thus, in order to synthesize some potential biologically interesting fluorinated derivatives of 5-benzylbarbituric acids, we decided to examine the chemistry of difluoro ketene aminal building block **103** with 5-benzylidene-1,3-dimethylbarbituric acid **125**. This resulted in not only the preparation of the expected initially formed cycloaddition products and eventual Michael addition products, but also the observation of additional cyclization and tautomerization chemistry which is apparently unique to the barbituric acid system.

5.4.1 Results and Discussion

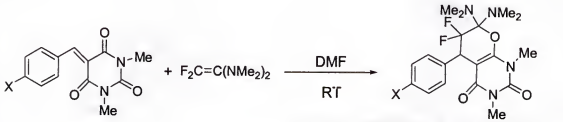
5-Benzylidene-1,3-dimethyl-barbituric acids **125a-d** were prepared in excellent yield by refluxing equimolar amounts of 1,3-dimethylbarbituric acid and the appropriate p-substituted benzaldhyde in 95% ethanol for 5-10 minutes[171] (Figure 5-11).



125a, X = H (92%); **b**, X = OCH_3(93%)
c, X = F (95%); **d**, X =Br (90%)

Figure 5-11. Preparation of 5-benzylidene-1,3-dimethyl-barbituric acids.

The reactions of **125a-d**, in DMF at room temperature, with a hexane solution of difluoroketene aminal **103**, gave the expected hetero-Diels-Alder products **126a-d** (Figure 5-12).



126a, X = H(87%); **b**, X = OCH_3(93%)
c, X = F(90%); **d**, X =Br(88%).

Figure 5-12. Hetero-Diels-Alder reaction of difluoroketene aminal with 5-Benzylidene-1,3-dimethyl-barbituric acids

The structures of **126a-d** were assigned on the basis of their NMR spectra, and confirmed by elemental analysis. In the ^{19}F NMR spectra of **126a-d** the two fluorine siganals appear as a well-separated AB system (i.e., δ= -77.1 and –93.2 ppm for **126**a). The signals for the single methine group in the ^{1}H spectra were typically observed as a doublet of doublets at about 5.30 ppm.

Cycloadducts **126a-d** underwent hydrolysis within 10 minutes at room temperature upon treatment with minimal amounts of 36% HCl in methylene chloride to give the formal Michael addition amide products **127a-d** (Figure 5-13). Longer stirring led to hydrolysis of the amides to the acids. Indeed, refluxing the amides for 2 hours under the same 36%HCl/CH_2Cl_2 conditions led to formation of the respective carboxylic acids **128a-d** in excellent yield. Most notable in the ^{1}H NMR spectra of the amide were their two methine signals (i.e. at 4.38 and 4.61 ppm, for **127a**), the latter signal being strongly (18 Hz) coupled to the CF_2 group. The fluorine signals appear in the ^{19}F NMR as a much less separated AB system (i.e., at δ -96.6 and –98.2 ppm, for **127a**). The fluorine AB systems of the carboxylic acids were shifted to considerably lower fields (i.e. δ -102.8 and –105.3 ppm for **128a**). As revealed by elemental analysis, three of the carboxylic acids **128a-c** incorporated a molecule of water upon recrystallization (Table 5-2).

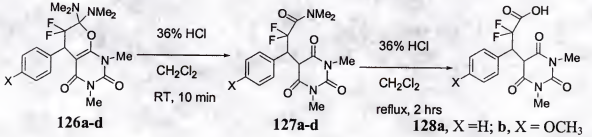


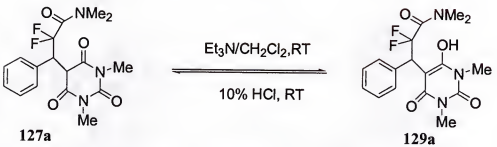
Figure 5-13. Hydrolysis of cycloadducts.

Unlike N,N-dimethylbarbituric acid itself, the enol forms of 5-substituted barbituric acids are of comparable stability to their keto forms.[172] In the case of amide **127a**, either tautomer could be obtained by control of the conditions. It could be

converted completely to its enol form **129a** by treatment with triethylamine. The proton NMR spectrum of the enol-amide was notable for its single, relatively low field methine signal at 5.42 ppm. Although the other amides were not attempted, presumably they also would have been similarly converted. Upon treatment of this enol with 10% HCl, it was transformed back to its keto form (Figure 5-14).

Table 5-2. Yield of substrates and products (%)

X	Substrate		Cycloadduct		Amide		Acid		Enol-Amide		Lactone	
H	**125a**	92	**126a**	87	**127a**	84	**128a**	89	**129a**	93	**130a**	89
OCH_3	**125b**	93	**126b**	93	**127b**	87	**128b**	81	-	-	**130b**	93
F	**125c**	95	**126c**	90	**127c**	86	**128c**	86	-	-	**130c**	90
Br	**125d**	90	**126d**	88	**127d**	82	**128d**	80	-	-	**130d**	91



127a **129a**

Figure 5-14. Isomerization of *gem*-difluorinated barbituric acid derivatives.

In a reaction which has little precedent,[173-175] the carboxylic acids **128a-d** underwent cyclization to the fused lactones **130a-d** in excellent yields upon treatment with acetic anhydride. Since the enol form of **128** is readily accessible, the observed lactonization process should not be surprising. The proton NMR spectra of these novel

barbiturate derivatives were also notable for their single methine signals at 4.7 ppm. Again, as was the case for the other cyclized system **126**, the fluorine AB signals observed for the lactones were also much more significantly separated (i.e. –100.8 and –116.8 ppm, for **130a**) than were the AB signals for the non-cyclized products **127**, **128**, and **129** (Figure 5-15). The lactones were observed to be very sensitive to moisture.

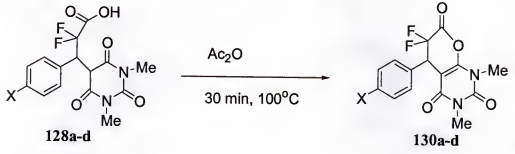


Figure 5-15. Lactonization

5.4.2 Biological activity

All of the cycloadducts **126a-d** and the amides **127a-d** were, upon request, submitted for screening as potential anticancer agents by the National Cancer Institute (NIH). Unfortunately, in a recent report provided to us, none of these compounds exhibited sufficient anti-cancer activity to warrant further action by the NCI. The other derivatives have not yet been tested.

In conclusion, difluoro ketene aminal **103** is a readily prepared, highly nucleophilic *in situ* reagent which undergoes specific [2+4] cycloadditions with α,β-unsaturated aldehydes and ketones and specific [2+2] cycloadditions with α,β-unsaturated esters and nitriles. Both types of adducts proved to be readily converted, by

mild hydrolysis, to the overall Michael addition products. It has been possible to utilize difluoro ketene aminal **103** to prepare a number of difluoro barbituric acid derivatives through hetero-Diels-Alder cycloadditions which lead, upon hydrolysis, to Michael-type products. Additional chemistry was described, including formation of novel lactone derivatives.

5.5 Experimental

5.5.1 General Procedure for Cycloadditions

To a solution of 1,1-bis(dimethylamino)-2,2,2-trifluoroethane (1.7g, 10mmol) in hexane (10mL) at –78°C under nitrogen was added n-BuLi (2.5M in hexanes, 4.5 mL), after which the reaction mixture was allowed to warm to room temperature and stirred for 10 hours. Then the reaction mixture was distilled at reduced pressure into a dry ice/acetone-cooled receiving flask (100mL, round bottom) equipped with rubber septum, magnetic stirr bar, and a water-cooled condenser. Before and after distillation, the apparatus was maintained under a dry nitrogen atomsphere. Substrate (14mmol) was added via syringe to this distillate, which contained the 1,1-bis(dimethylamino)-2,2-difluoroethene (**103**), and the reaction mixture was stirred at room temperature or given temperature for the required time. The time required for each reaction was determined by following the reactions by ^{19}F NMR. The products were isolated by distillation under reduced pressure. The yields are reported with respect to the 1,1-bis(dimethylamino)-2,2,2-trifluoroetane.

2,2-Bis(dimethylamino)-3,3-difluoro-2H-pyran, **112a**: reaction was complete after 5 min at rt (70%); bp 57-58°C/1.5 Torr; ^{1}H NMR ($CDCl_3$) δ 2.31 (ddt, J=2.0, 3.7, 15.4 Hz), 2.47 (t, J =1.2 Hz, 12H), 4.25-4.32 (m, 1H), 5.99-6.04 (m, 1H); ^{19}F NMR δ –101.2 (t, J =171. Hz); ^{13}C NMR δ 32.5 (t, J= 25.2 Hz), 38.6, 97.8, 99.6 (t, J=24.2 Hz), 141.7, 123.0 (t, J=256.8 Hz); HRMS (CI) calcd for $C_9H_{16}F_2N_2O$ 207.1309, found 207.1309. Anal. Calcd for $C_9H_{16}F_2N_2O$: C, 52.43; H, 7.77; N, 13.60. Found: C, 52.31; H, 8.10; N, 13.50.

2,2-Bis(dimethylamino)-3,3-difluoro-6-methyl-2H-pyrane, **112b**: reaction was complete after 5 min at rt (72%); bp 62-63°C/1.5Torr; ^{1}H NMR ($CDCl_3$) δ 1.59 (m, 3H), 2.35 (th, 2H), 2.49 (t, J=1.2 Hz, 12H), 4.14 (m, 1H); ^{19}F NMR δ –102.6 (t, J=14.2 Hz); ^{13}C NMR δ 18.8, 32.7 (t, J=25.7 Hz), 38.7, 93.4, 123.1 (t, J=256.3 Hz), 99.3, 149.0; HRMS (EI) calcd for $C_{10}H_{19}F_2NO$ 221.1465, found 221.1454. Anal. Cald for for $C_{10}H_{18}F_2N_2O$: C, 54.55; H, 8.18; N, 12.73. Found: C, 54.66; H, 8.49; N, 12.83.

Methyl 2,2-bis(dimethylamino)-3,3-difluorocyclobutanecarboxylate, **113a**: reaction was complete after 3 min. at rt (87%); bp 92-93°C/1.8 Torr, ^{1}H NMR ($CDCl_3$) δ 2.05-2.21 (m, 1H), 2.41 (s, 6H), 2.50 (s, 6H), 2.69-2.88 (m, 1H), 2.96 (ddd, 1H, J = 13.7, 8.5, 3.9 Hz); ^{19}F NMR δ –94.9 (ddd, J = 190.4, 12.1, 7.3 Hz); -101.7 (ddd, J= 190.4, 17.1, 14.7 Hz); ^{13}C NMR δ 35.5 (td, J = 23.2, 3.0 Hz), 40.7, 51.6 (q, J = 5.6Hz), 92.6 (t, J = 21.1 Hz), 121.7 (dd, J = 300.5, 280.5 Hz), 170.9; HRMS (CI) calcd for $C_{10}H_{19}F_2N_2O_2$ 237.1415, found 237.1458.

Methyl 2,2-bis(dimethylamino)-3,3-difluoro-1-1methyl-cyclobutanecarboxylate, **113b**: reaction was complete after 10 min at 90 °C (84%); bp 92-93°C/ 1.5 Torr, ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 9H), 1.92 (ddd, 1H, J =16.2, 13.7, 2.7 Hz), 2.35 (s, 6H), 2.59 (s, 6H), 2.95-3.18 (m, 1H), 3.31 (s, 3H); ^{19}F NMR δ –93.7 (dd, J = 200.2, 12.2 Hz), -95.0 (ddd, J = 197.8, 19.5, 17.1 Hz),; ^{13}C NMR δ 23.0, 40.8, 41.6, 46.9, 51.9, 93.4 (t, J= 17.2 Hz), 121.9 (dd, J = 289.7, 298.9 Hz), 174.5; HRMS (CI) calcd for $C_{11}H_{20}F_2N_2O_2$ 250.1493, found 250.1504.

2,2-Bis(dimethylamino)-3,3-difluorocyclobutanecarbonitrile, **114a**: reaction was complete after 3 min at rt (84%); bp 92-93°C/0.6 Torr; ^{1}H NMR ($CDCl_3$) δ 2.10-2.30 (m, 8H), 2.42 (s, 6H), 2.55-2.65 (m, 1H); ^{19}F NMR δ –98.1 (ddd, J= 190.8, 9.8, 7.3 Hz), -101.8 (dt, J= 190.8, 17.1 Hz); ^{13}C NMR δ 26.1, 35.3 (t, J = 24.2 Hz), 41.0, 90.9 (t, J= 20.6 Hz), 118.7, 119.5 (dd, J= 293.6, 286.1 Hz), HRMS (CI) calcd for $C_{19}H_{16}F_2N_3$ 204.1312, found 204.1311.

2,2-Bis(dimethylamino)-3,3-difluoro-1-methylcyclobutanecarbonitrile, **114b**: recation was complete after 10 min at 90 °C (46%); bp 110-112°C/ 0.6 Torr; ^{1}H NMR ($CDCl_3$) δ 1.18 (s, 3H), 1.68 (ddd, 1H, J= 18.8, 13.2, 7.3 Hz), 2.24 (s, 6H), 2.38-2.44 (m, 7H); ^{19}F NMR δ –93.9 (ddd, J = 202.6, 14.6, 17.1 Hz), -94.8 (ddd, J = 200.2, 9.8, 7.3 Hz); ^{13}C NMR δ 22.7, 33.8, 40.5, 41.9, 42.8 (t, J = 23.2 Hz), 92.7 (t, J=18.1 Hz), 122.1, 120.8 (dd, J = 291.6, 294.6 Hz), HRMS (CI) calcd for $C_{10}H_{17}F_2N_3$ 217.1391, found 217.1420.

5.5.2 General Procedure for Hydrolysis Reaction

Cycloadduct (1mmol) was dissolved in 20 mL of methylene chloride, and 0.5 mL of 3% HCl solution was added to the solution. The reaction mixture was stirred for 2-5 hours at room temperature, and then 30 mL of ether was added. The organic layer was washed with water and dried. Then the ether was removed, and the residue was distilled at reduced pressure to give the product. If the reaction mixture was allowed to stir for too long, a side reaction occurred leading to a product which was difficult to separate.

N,N-Dimethyl 2,2-Difluoro-4-oxobutanoamide, **115a**. A portion of 1.19g (15mmol) of 2a and 30 mL of methylene chloride were combined in a 100 mL flask. Then 5 mL of 3% HCl solution was added. And the PH control to 5. The mixture was stirred for 1 hour, and then 30 mL of ether was added. The layer was washed with saturated sodium carbonate (10mL x 2) and brine and then dried with $MgSO_4$. Removal of solvent gave crude fluorinated aldehyde **115a**: ^{1}H NMR δ 2.16-2.50 (m, 5H), 2.56 (t, 3H, J=1.9Hz), 9.20 (m, 1H); ^{19}F NMR δ –99.8 (t, J =17.1 Hz).

The crude aldehyde was treated directly with 0.1 M of 2,4-dinitrophenylhydrazine solution to give yellow crystals of the 2,4-dinitrophenylhydrazone, in 83% yield. mp 138-140 °C. ^{1}H NMR ($CDCl_3$) δ 2.28-2.52 (m, 7H), 2.60 (t, J=1.9Hz), 5.96 (t, J=4.2 Hz), 7.20-7.78 (m, 2H), 10.32 (s, 1H); ^{19}F NMR δ –99.8 (t, 2F, J=17.1 Hz); ^{13}C NMR δ 25.7 (t, J=5.1 Hz, 31.6 (t, J=22.9 Hz), 36.2, 115.9, 119.9 (t, J=255.4 Hz), 130.1, 144.7, 149.3, 162.5 (t, J =29.1 Hz); HRMS (CI) calcd for $C_{13}H_{16}F_2N_5O_5$ 360.1119, found 260.1113. Anal. Calcd. for $C_{13}H_{15}F_2N_5O_5$: C, 43.45; H, 4.18; N, 19.50. Found: C, 43.84; H, 4.06; N, 19.43.

N,N-Dimethyl 2,2-difluoro-4-oxopentanoamide, **115b**: reaction was complete after 2 hours (89%); bp 95-97°C/ 1.5 Torr; ^{1}H NMR ($CDCl_3$) δ 1.57 (s, 3H), 2.30-2.58 (m, 7H), 2.59 (t, J=3.2 Hz, 3H); ^{19}F NMR δ –99.5 (t, J =19.5 Hz); ^{13}C NMR δ 29.1, 29.4, 29.7, 36.0 (m), 119.9 (t, J= 19.5 Hz), 162.4 (t, J = 14.1 Hz), 204.1; HRMS (CI) cald for $C_8H_{14}F_2NO_2$ 194.0993, found 194.0998. Anal. Calcd for $C_8H_{14}F_2NO_2$: C: 49.74; H, 6.74; N, 7.25. Found: C, 49.41; H, 6.78; N, 7.59.

N,N-Dimethyl 4-carbomethoxy-2,2-difluorobutanoamide, **116a**: reaction was complete after 2 hours (82%); bp 109-110°C/ 3.0 Torr; ^{1}H NMR ($CDCl_3$) δ 2.42-2.62 (m, 4H), 2.98 (s, 3H), 3.16 (t, 3H, J = 1.9 Hz), 3.68 (s, 3H); ^{19}F NMR δ –101.1 (t, J = 17.1 Hz); ^{13}C NMR δ 26.7, 29.9 (t, J = 24.2 Hz), 36.7 (t, J =7.1 Hz), 36.5 (t, J=7.1 Hz), 51.6 (q, J= 4.5 Hz), 118.6 (t, J =7.1 Hz), 162. 5 (t, J = 28.7 Hz), 172.3; HRMS calcd for $C_8H_{14}F_2NO_3$ 210.0942, found 210.0979. anal. Calcd for $C_8H_{13}F_2NO_3$: C, 45.93; H, 6.22; N, 6.70. Found: C, 46.40; H, 6.45; N, 7.25.

N,N-Dimethyl 4-carbomethoxy-2,2-difluoro-4-methtylbutanoamide, **116b**: recation was complete after 5 hours (89%); bp 105-106°C/ 2.3 Torr; ^{1}H NMR ($CDCl_3$) δ 1.06 (d, 3H, J = 7.5 Hz), 2.07-2.27 (m, 1H), 2.70-2.90 (m, 2H), 2.60 (t, 3H, J=2.3 Hz), 2.47 (3H), 3.36 (s, 3H); ^{19}F NMR δ –98.9 (ddd, J= 280.8, 21.9, 14.7 Hz), -100.3 (ddd, J =280.8, 19.5, 17.1 Hz); ^{13}C NMR δ 18.6, 34.1, 36.4, 38.5 (t, J=23.2 Hz), 51.6 (q, J=7.6 Hz), 175.8, 162.8 (t, J=28.7 Hz), 19.4 (t, J =255.3 Hz). HRMS (CI) cald for $C_9H_{15}F_2NO_3$ 224.1098, found 224.1097. Anal Calcd for $C_9H_{15}F_2NO_3$: C, 48.43; H, 6.73; N, 6.28. Found: C. 48.14; H,7.27; N, 6.57.

N,N-Dimethyl 4-cyano-2,2-difluorobutanoamide, **117a**: reaction was complete after 2 hours (85%); bp 114-115°C/2.5 Torr; ^{1}H NMR ($CDCl_3$) δ 2.55 (t, J = 2.2 Hz, 3H), 2.46 (t, J =1.0 Hz, 3H), 1.90-2.20 (m, 4H); ^{19}F NMR δ –101.1 (t, J =17.2 Hz); ^{13}C NMR δ 10.6 (t, J= 6.6 Hz), 31.1 (t, J =24.7 Hz), 36.3 (m), 118.3 (t, J=256.8 Hz), 161.8 (t, J =28.1 Hz); HRMS (CI) cacld for $C_7H_{11}F_2N_2O$ 177.0839, found 177.0851. Anal. Calcd for $C_7H_{10}F_2N_2O$: C, 47.73; H, 5.68; N, 15.91. Found: C, 48.19; H, 5.97; N, 16.27.

N,N-Dimethyl 4-cyano-2,2-difluoro-4-methylbutanoamide, **117b**: recation was complete after 5 hours; bp 105-106°C/2.3 Torr; ^{1}H NMR ($CDCl_3$) δ 1.06 (d, 3H, J=7.5 Hz), 2.07-2.27 (m, 1H), 2.70-2.90 (m, 2H), 2.60 (t, 3H, J=2.3 Hz), 2.47 (3H), 3.36 (s, 3H); ^{19}F NMR δ –98.9 (ddd, J=280.8, 21.9, 14.7 Hz), -100.3 (ddd, J = 280.8, 19.5, 17.1 Hz), ^{13}CNMR δ 18.6, 19.6 (t, J =4.0 Hz), 36.4, 38.8 (t, J=23.7 Hz), 118.4 (t, J=257.3 Hz), 121.9, 162.1 (t, J= 28.2 Hz); HRMS (CI) calcd for $C_8H_{12}F_2NO$ 190.0918, found 190.0915. Anal. Calcd for $C_8H_{12}F_2NO$: C, 50.53; H, 6.32; N, 14.74 Found: C, 50.14; H, 6.78; N, 14.70.

5.5.3 Synthesis of Monofluoro-Aminopyridine

N,N,5,6-tetramethyl-3-fluoro-2-pyridineamine, **118a**

3.4mL of MeLi and LiBr complex solution (1.5M in ether) was added dropwise to 1.0g of compound 1 in 10mL of THF under nitrogen at 0°C. Then the reaction mixture was stirred for 2.5 hours at room temperature. ^{19}F NMR spectra showed that the starting material was gone. 50mL of ether was added and washed with water (10ml X 2), dried

with $MgSO_4$. Evaporation of the ether gave yellow oil and purified by column chromatography (hexane:ethyl acetate=10:1) to give yellow liquid 0.69g (81%). ^1H NMR δ 2.12 (s, 1H), 2.33 (s, 3H), 3.00 (s, 3H), 3.01 (s, 3H), 6.93 (d, 1H, J=13.7 Hz). ^{19}F NMR δ -135.21 (d, J=13.7Hz). ^{13}C NMR δ 17.65, 21.55, 39.83, 39.91, 121.36, 124.44 (d, J=18.3 Hz), 147.32 (d, J=5.7 Hz), 148.83 (d, J=4.6 Hz), 147.59 (d, J=253.1 Hz) ppm. IR (neat): 2954.3, 2929.9, 2858.0, 2789.2, 1610.3, 1575.9, 1500.2, 1424.5, 1362.6, 1231.9, 1176.8, 1094.3, 997.9, 947.9, 887.8, 798.4, 743.4 cm^{-1}. HRMS (CI) Calcd. for $C_9H_{14}FN_2$ (M+1): 168.1063; Found: 168.1058. Elem. Anal. Calcd. For $C_9H_{13}FN_2$: C 64.29%; H 7.74%; N 16.67%. Found: C 64.04%; H 7.98%; N 16.62%.

N,N,5-trimethyl-6-butyl-3-fluoro-2-pyridineamine, **118b**

Procedure same as above. Yield: 42%. ^1H NMR δ 0.87 (t, 3H, J=7.3 Hz), 1.30 (hexset, 2H, J=7.3 Hz), 1.58 (P, 2H, J=7.3 Hz), 2.09 (s, 3H), 2.53 (t, 2H, J=7.3 Hz), 2.93 (d, 6H, J=1.7 Hz), 6.87 (d, 1H, J=13.7 Hz). ^{19}F NMR δ -136.02 (d, J=13.7 Hz). ^{13}C NMR δ 14.05, 17.36, 22.61, 30.58, 34.08, 39.98, 40.03, 121.04, 124.74 (d, J=19.5 Hz), 147.33 (d, J=5.8 Hz), 147.42 (d, J=253.1 Hz), 152.61 (d, J=4.5 Hz) ppm. IR (neat): 2957.0, 2929.9, 2860.4, 2797.8, 1613.4, 1570.6, 1496.8, 1464.9, 1424.1, 1366.4, 1238.5, 1182.0, 1090.9, 1018.5, 955.6, 888.0, 805.0, 750.7 cm^{-1}. HRMS (CI) Calcd. for $C_{12}H_{20}N_2F$ (M+1): 211.1611; Found: 211.1607.

N,N,5-trimethyl-3-fluoro-6-phenyl-2-pyridineamine, **118c**

Procedure same as above. Yield: 46%. ^1H NMR δ 2.12 (s, 3H), 2.93 (d, 6H, J=1.95 Hz), 6.95 (d, 1H, J=13.6 Hz), 7.16-7.31 (m, 3H), 7.40-7.45 (m, 2H). ^{19}F NMR δ -133.59 (d,

J=13.6 Hz). ^{13}C NMR δ 18.83, 39.84 (m), 120.96 (d, J=3.0 Hz), 125.56 (d, J=18.1 Hz), 127.35, 127.77, 129.12, 140.45, 147.57 (d, J=7.1 Hz), 148.16 (d, J= 256.8 Hz), 150.24 (d, J=4.5 Hz) ppm. IR (neat): 2942.7, 2872.2, 1607.6, 1560.6, 1495.9, 1425.4, 1360.8, 1225.6, 1190.4, 1114.0, 1002.4, 949.5, 884.8, 779.1, 737.9, 696.8, 661.5, 561.6, 497.0 cm^{-1}. HRMS (CI) Calcd. for $C_{14}H_{16}N_2F$ (M+1): 231.1297; Found, 231.1250. Elem. Anal. For $C_{14}H_{16}N_2F$ C 73.04, H 6.52, N 12.17; Found: C 72.91, H 6.58, H 11.81.

N,N,5-trimethyl-6-t-butyl-3-fluoro-2-pyridineamine, **118d**

Procedure same as above. Yield: 24%. ^{1}H NMR δ 1.40 (s, 9H), 2.37 (s, 3H), 3.04 (s, 6H), 6.93 (d, J=14.0Hz). ^{19}F NMR δ -137.07 (d, J=14.0Hz). ^{13}C NMR δ 21.19, 29.84, 38.82, 39.78, 39.85, 121.03, 127.29 (d, J=19.1 Hz), 145.21 (d, J=6.1 Hz), 146.75 (d, J=254.8 Hz), 157.70 (d, J=4.5 Hz) ppm. IR (neat): 2940.6, 2858.0, 2789.2, 1610.3, 1575.9, 1494.3, 1424.5, 1341.9, 1231.9, 1183.7, 1169.9, 1080.5, 997.9, 942.9, 887.8, 750.2 cm^{-1}. HRMS (EI) Calcd. for $C_{12}H_{20}N_2F$: 210.1532; Found: 210.1535.

5.5.4 1,3-Dipolar cycloaddition reaction

5.5.4.1 General synthesis of nitrones

Compounds **121**a-d were obtained according to a described method by condensing the appropriate substituted benzaldehyde (10 mmol) with phenylhydroxylamine (10 mmol) dissolved in absolute ethanol (5 mL) and the reaction mixture was stirred for few minutes. The precipitate was filtered off, washed with cooled ethanol and dried, to yield compounds 3a-d (85-92%).

α-4-Fluorophenyl-N-phenylnitrone, **121b**

Yield: 88%. ^{1}H NMR: 7.16 (t, J =8.8 Hz, 2H), 7.42-7.54 (m, 3H), 7.72-7.80 (m, 2H), 7.90 (s, 1H), 8.45 (dd, J =9.0, 5.6 Hz, 2H); ^{19}F NMR: -107.17 (m, 1F).

α-4-Methoxyphenyl-N-phenylnitrone, **121c**

Yield: 86%; ^{1}H NMR: 3.87 (s, 3H), 6.98 (d, J = 8.8 Hz, 2H), 7.42-7.50 (m, 3H), 7.74-7.80 (m, 2H), 8.01 (s, 1H), 8.40 (d, J = 8.8 Hz, 2H).

α-2-Methylphenyl-N-phenylnitrone, **121d**

Yield: 85%; ^{1}H NMR: 2.44 (s, 3H), 7.20-7.28 (m, 1H), 7.30-7.38 (m, 2H), 7.42-7.52 (m, 3H), 7.70-7.80 (m, 2H), 8.06 (s, 1H), 9.35-9.39 (m, 1H).

5.5.4.2 General procedure for 1,3-dipolar cycloaddition reaction

To a solution of 1,1-bis(dimethylamino)-2,2,2-trifluoroethane (1.7g, 10 mmol) in hexane (10mL) at 0oC under nitrogen was added n-BuLi (2.5 M in hexanes, 4.5 mL), after which the reaction mixture was allowed to warm to room temperature and stirred 10 hours. Then the reaction mixture was distilled at reduced pressure into a dry ice/acetone-cooled receiving flask (100mL, round bottom) equipped with rubber septum, magnetic stir bar, and water-cooled condenser. Before and after distillation, the apparatus was maintained under a dry nitrogen atmosphere. α-substituted-phenyl-N-phenylnitrone (7mmol) in 2-3 mL of dry DMF was added. The reaction mixture was refluxed for 24 hours under dried nitrogen. ^{19}F NMR spectra of the crude mixture showed that the starting material was consumed, a new multiple peak at –105.25- -105.40 ppm came out.

Ether (10 mL) was added, and the mixture was washed with brine, dried to get yellow solid. Column chlomotography (9:2 hexane: ethyl acetate) gave yellow solid, and recrystallized from methylene chloride. The yields are reported with respect to the nitrones.

2,2-Difluoro-N,N-dimethyl-3-phenylamino-3-phenyl-propioamide, **122a**

Yield: 56%; mp 138-140°C; ^{1}H NMR 2.95 (s, 3H), 2.86 (t, J = 1.8 Hz, 3H), 5.05 (s, 1H), 5.14 (t, J =11.4 Hz, 1H), 6.60-6.67 (m, 2H), 6.71 (tt, J =7.8, 0.6 Hz, 1H), 7.28-7.40 (m, 3H), 7.08-7.18 (m, 2H), 7.48-7.54 (m, 2H). ^{19}F NMR –102.11 (dd, J = 273.2, 10.7 Hz, 1F), -105.83 (dd, J = 273.2, 12.8 Hz, 1F). ^{13}C NMR 36.9 (dd, J = 8.6, 6.6 Hz), 37.22, 61.44 (t, J = 25.2 Hz), 113.82, 116.69 (t, J = 260.4 Hz), 118.34, 128.38, 128.44, 128.66, 129.15, 135.13 (d, J = 2.5 Hz), 146.00, 162.00, 162.65 (t, J =28.2 Hz) ppm. HRMS (CI) Calcd. for $C_{17}H_{18}ON_2F_2$: 304.1387; Found: 304.1321. Element. Anal. Calcd. for $C_{17}H_{18}ON_2F_2$: C 67.11, N 9.21, H 6.58; Found: C 67.02, N 9.25, H 6.35.

2,2-Difluoro-N,N-dimethyl-3-(4-fluorophenyl)amino-3-phenyl-propioamide, **122b**

Yield: 50%; mp 125-126°C; ^{1}H NMR 2.96 (s, 3H), 3.03 (t, J =2.1 Hz, 3H), 5.13 (dd, J =13.4, 10.3 Hz, 1H), 6.62 (d, J = 8.8 Hz, 2H), 6.72 (t, J = 6.8 Hz, 1H), 7.04 (t, J 8.3 Hz, 2H), 7.13 (t, J = 8.1 Hz, 2H), 7.50 (dd, J = 8.3, 5.4 Hz, 2H); ^{19}F NMR –101.96 (dd, J =273.2, 8.50 Hz, 1F), -105.39 (dd, J = 273.2, 12.8 Hz, 1F), -114.17 (m, 1F); ^{13}C NMR 36.97 (dd, J = 8.6, 6.0 Hz), 37.20, 60.92 (t, J =25.20 Hz), 113.86, 115.34 (d, J = 21.7 Hz), 116.49 (t, J = 261.9 Hz), 118.58, 129.22, 130.48 (d, J = 8.1 Hz), 130.90 (t, J =2.1 Hz),

145.80, 162.48 (t, J = 28.2 Hz), 162.69 (d. J = 247.3 Hz) ppm; HRMS (CI) Calcd. for $C_{17}H_{18}ON_2F_3$ (M+1): 323.1371; Found: 323.1384.

2,2-Difluoro-N,N-dimethyl-3-(4-methoxyphenyl)amino-3-phenyl-propioamide, **122c** Yield: 52%, mp: 120-123°C; ^{1}H NMR 2.93 (s, 3H), 2.97 (t, J =2.4 Hz, 3H), 3.78 (s, 3H), 5.07 (dd, J =13.7, 10.3 Hz, 1H), 6.61 (d, J 8.6 Hz, 2H), 6.69 (t, J 7.3 Hz, 1H), 6.87 (d, J =8.8 Hz, 2H), 7.11 (dd, J = 8.5, 7.3 Hz, 2Hz), 7.41 (d, J = 8.6 Hz, 2H); ^{19}F NMR – 102.43 (dd, J =271.0, 10.7 Hz, 1F), -105.82 (dd, J = 271.0, 12.8 Hz, 1F); ^{13}C NMR 36.97 (dd, J = 8.6, 6.6 Hz), 37.25, 55.18, 60.91 (t, J =24.7 Hz), 113.78, 113.83, 116.67 (t, J =259.9 Hz), 118.27, 126.96 (d, J =2.5 Hz), 129.14, 129.81, 146.07, 159.58, 162.76 (t, J = 28.7 Hz). HRMS (CI) Calcd. for $C_{18}H_{21}O_2N_2F_2$ (M+1) : 335.1571; Found: 335.1512.

2,2-Difluoro-N,N-dimethyl-3-(2-methylphenyl)amino-3-phenyl-propioamide, **122d** Refluxed for 48 hours. Yield: 38%; mp: 129-132°C ; ^{1}H NMR 2.43 (s, 3H), 2.86 (t, J = 1.5 Hz, 3H), 2.88 (s, 3H), 4.62-4.86 (br, 1H), 5.42 (dd, J =16.1, 7.8 Hz, 1H), 6.51 (dd, J = 8.3, 1.2 Hz, 2H), 6.61 (t, J =7.3 Hz, 1H), 7.03 (t, J = 7.3 Hz, 2H), 7.08-7.14 (m, 3H), 7.39-7.45 (m, 1H); ^{19}F NMR –101.13 (dd, J = 171.0, 6.4 Hz, 1F), -108.83 (dd, J = 271.0, 14.9 Hz, 1F); ^{13}C NMR 19.82, 30.81, 36.92 (dd, J = 9.6, 5.0 Hz), 37.37, 56.74 (t, J = 25.2 Hz), 113.66, 117.34 (t, 258.4 Hz), 118.36, 126.23, 127.33, 128.21, 129.14, 130.56, 133.74, 137.42, 146.05, 162.90 (t, J = 28.2 Hz). HRMS (CI) Calcd. for $C_{18}H_{20}ON_2F_2$ (M+1) : 318.1544; Found: 318.1512.

5.5.5 Synthesis of *gem*-Difluorinated Barbituric Acid Derivatives

5.5.5.1 General procedure for the synthesis of 1,3-dimethyl-barbiturylbenzylidenes

Compound **125** were obtained according to a described method by condensing benzaldhyde (20mmol) with 1,3-dimethylbarbituric acid (20mmol) dissolved in hot 95% ethanol (20mL). The precipitate was filtered off, washed with cooled ethanol and dried, to yield compound 3 (95%).

5-Benzylidene-1,3-dimethylbarbituric acid , **125a**

Yield: 92%; ^{1}H NMR (DMSO-d_6) δ 3.18 (s, 3H), 3.23 (s, 3H), 7.43-7.58 (m, 3H), 8.02 (d, 2H, J=6.8 Hz), 8.35 (s, 1H) ppm.

5-(4-methoxyphenyl)-1,3-dimethylbarbituric acid, **125b**

Yield: 93%; ^{1}H NMR (DMSO-d_6) δ 3.19 (s, 3H), 3.21 (s, 3H), 3.87 (s, 3H), 7.05 (d, 2H, J=9.0 Hz), 8.32 (d, 2H, J=9.0 Hz), 8.30 (s, 1H) ppm.

5-(4-fluorophenyl)-1,3-dimethylbarbituric acid, **125c**

Yield: 95%: ^{1}H NMR (DMSO-d_6) δ 3.38 (s, 3H), 3.41 (s, 3H), 7.15 (t, 2H, J=8.79 Hz), 8.19 (dd, 2H, J=8.79, 5.8 Hz), 8.51 (s, 1H) ppm. ^{19}F NMR (DMSO-d_6) δ -103.81 (m, 1F) ppm.

5-(4-bromophenyl)-1,3-dimethylbarbituric acid, **125d**

Yield: 90%; ^{1}H NMR (DMSO-d_6) δ 3.37 (s, 3H), 3.42 (s, 3H), 7.60 (d, 2H, J=8.5 Hz), 7.93 (d, J=8.5 Hz), 8.47 (s, 1H) ppm.

5.5.5.2 General procedure for the synthesis of compound **126**

To a solution of 1,1-bis(dimethylamino)-2,2,2-trifluoroethane (1.7g, 10mmol) in hexane (10mL) at 0°C under nitrogen was added n-BuLi (2.5 M in hexanes, 4.5 mL), after which the reaction mixture was allowed to warm to room temperature and stirred 10 hours. Then the reaction mixture was distilled at reduced pressure into dry ice/acetone-cooled receiving flask (100mL round bottom flask) equipped with rubber septum, magnetic stirr bar, and a water-cooled condenser. Before and after distillation, the apparatus was maintained under a dry nitrogen atomsphere. 5-Benzylidene-1,3-dimethylbarbituric acid (8mmol) in 3mL of N,N-dimethylforamide was added. The reaction mixture was stirred for 10 minutes at room temperature under dried nitrogen. The viscous solid was filtered and washed with hexane till the solid became powder and recrystallized in methylene chloride. The yields are reported with respect to the 5-Benzylidene-1,3-dimethylbarbituric acid.

7,7-bis(dimethylamino)-6,6-difluoro-1,3-dimethyl-5-phenyl-1,3,4,5,6,7-hexahydro-2*H*-pyrano[2,3-d]pyrimidine-2,4-dione, **126a**

Yield: 87%; mp 198-200°C; ^{1}H NMR ($CDCl_3$) δ 3.06-3.32 (b, 18H), 5.28 (dd, 1H, J=32.7, 10.4 Hz), 7.25 (m, 3H), 7.65 ppm (d, 2H, J=6.8 Hz). ^{19}F NMR δ -77.06 (d, J=268.6 Hz), -93.30 ppm (dd, J=268.6, 31.7 Hz). ^{13}C NMR δ 27.15, 44.25, 46.49 (t, J=22.9 Hz), 80.05 (d, J=9.2 Hz), 121.23 (dd, J=268.0 Hz, 255.4 Hz), 126.55, 127.52, 130.36, 137.45, 152.48, 162.71, 164.43 (t, J=28.6 Hz). HRMS (EI) Calcd for $C_{19}H_{24}F_2N_4O_3$: 394.1816, Found: 394.1869. Anal. Calcd for $C_{19}H_{24}F_2N_4O_3$: C, 57.87; H, 6.09; N, 14.21. Found: C, 57.97; H, 6.37; N, 14.30.

7,7-di(dimethylamino)-6,6-difluoro-1,3-dimethyl-5-(4'-methoxyphenyl)-1,3,4,5,6,7-hexahydro-2*H*-pyrano[2,3-d]pyrimidine-2,4-dione, **126b**

Yield: 93%; mp 204-207°C; ^{1}H NMR ($CDCl_3$) δ 3.04-3.40 (m, 18H), 3.74 (s, 3H), 5.30 (dd, J=29.9, 11.0 Hz), 6.80 (d, J=6.8 Hz), 7.62 (d, J=8.5 Hz). ^{19}F NMR δ -79.84 (d, J=273.5 Hz), -92.37 (dd, J=273.5, 29.3 Hz). ^{13}C NMR δ 27.51, 44.87, 47.03 (t, J=24.1 Hz), 55.07, 81.84, 113.24, 121.08 (dd, J=264.3, 255.6 Hz), 128.67, 131.63, 153.37, 158.60, 163.70, 167.02 (t, J=34.0 Hz). HRMS (CI) Cacld for $C_{20}H_{27}F_2N_4O_4$+H^+: 425.2000, Found: 425.1971. Anal. For $C_{20}H_{27}F_2N_4O_4$: C, 56.60; H, 6.13; N, 13.21. Found: C, 56.31; H, 6.29; N, 13.20.

7,7-di(dimethylamino)-6,6-difluoro-1,3-dimethyl-5-(4'-fluorophenyl)-1,3,4,5,6,7-hexahydro-2*H*-pyrano[2,3-d]pyrimidine-2,4-dione, **126c**

Yield: 90%; mp: 193-195°C; ^{1}H NMR ($CDCl_3$) δ 3.02-3.40 (b, 18H), 5.35 (dd, 1H, J=30.8, 10.4 Hz), 6.95 (t, 2H, J=8.79 Hz), 7.67 ppm (dd, 2H, J=8.51, 5.76 Hz). ^{19}F NMR δ -79.24 (dd, 1F, J=273.5, 5.3 Hz), -93.22 ppm (dd, 1F, J=273.5, 31.7 Hz), -116.35 (m, 1F). ^{13}C NMR δ 27.53, 44.95, 46.83 (t, J=22.9 Hz), 81.42 (d, J=8.0 Hz), 114.62 (d, J=20.6 Hz), 121.10 (dd, J=266.8, 256.5 Hz), 131.99 (d, J=8.0 Hz), 132.28 (d, J=3.5 Hz), 153.37, 160.29, 163.53, 163.71, 166.95 ppm (t, J=29.8 Hz). HRMS (EI) Cacld for $C_{19}H_{23}F_3N_4O_3$: 412.1722, Found: 412.1758. Anal. For $C_{19}H_{23}F_3N_4O_3$: C, 55.34; H, 5.58; N, 13.59. Found: C, 55.07; H, 5.65; N, 13.48.

7,7-di(dimethylamino)-6,6-difluoro-1,3-dimethyl-5-(4'-bromophenyl)-1,3,4,5,6,7-hexahydro-2*H*-pyrano[2,3-d]pyrimidine-2,4-dione, **126d**

Yield: 88%; mp: 185-187°C; ^{1}H NMR ($CDCl_3$) δ 3.21 (s, 18H), 5.29 (dd, J=31.3, 9.8 Hz), 7.37 (d, J=8.3 Hz), 7.54 ppm (d, J=8.3 Hz). ^{19}F NMR δ -79.08 (dd, J=273.4, 4.9 Hz), -93.79 ppm (dd, J=273.4, 31.7 Hz). ^{13}C NMR δ 27.52 (q, J=5.5 Hz), 44.97, 46.77 (td, J=20.2, 4.0 Hz), 81.08 (d, J=9.1 Hz), 120.99 (dd, J=263.9, 257.3 Hz), 130.89, 131.89, 135.57, 153.31, 163.65, 166.73 (t, J=28.4 Hz). HRMS (EI) Calcd for $C_{19}H_{23}BrF_2N_4O_3$: 472.0922. Found: 472.0925. Anal. For $C_{19}H_{23}BrF_2N_4O_3$: C, 48.20; H, 4.86; N, 11.84. Found: C, 48.09; H, 4.91; N, 11.90.

N,N-dimethyl-3-(1,3-dimethyl-2,4,6-trioxohexahydro-5-pyrimidiryl)-2,2-difluoro-3-phenylpropanamide, **127a**

Compound **126a** (1.71g, 4.3 mmol) was dissolved in 10 mL of methylene chloride and stirred at room temperature with 36% of HCl (0.2 mL) for 30 min.. ^{19}F NMR spectra showed that the reaction was finished. Methylene chloride (20mL) was added, and the reaction mixture was washed with water (2x10mL), and then dried by $MgSO_4$. The solvent was evaporated to give solid which was recrystallized in methylene chloride to give white solid 1.3g (84%).

Yield: 84%; mp: 109-110°C; ^{1}H NMR ($CDCl_3$) 2.95 (s,3H), 3.07 (s,3H), 3.18 (s, 3H), 3.21 (s, 3H), 4.38 (d, J=3.7 Hz, 1H), 4.61 (td, J=18.3, 3.7 Hz, 1H), 7.30 ppm (m, 5H). ^{19}F NMR -96.59 (dd, J=288.1, 19.5 Hz), -98.16 ppm(dd, J=288.1, 19.5 Hz). ^{13}C NMR 28.35, 28.43, 37.03 (t, J=7.6 Hz), 37.20, 50.57 (t, J=2.3Hz), 51.88 (t, J=24.4 Hz), 117.51 (dd, J=264.8, 259.4 Hz), 128.46, 128.65, 129.71, 132.58 , 150.86, 162.31 (t, J=27.5 Hz), 166.67, 166.96. HRMS (CI) Calcd for $C_{17}H_{20}F_2N_3O_4$: 368.1422. Found: 368.1417.

Element Anal. For $C_{17}H_{19}F_2N_3O_4$: C, 55.58; H, 5.21; N, 11.44. Found: C, 55.76; H, 5.26; N, 11.33.

N,N-dimethyl-3-(1,3-dimethyl-2,4,6-trioxohexahydro-5-pyrimidiryl)-2,2-difluoro-3-(4-methoxyphenyl) propanamide, **127b**

Yield: 87%; mp: 131-132°C; ^{1}H NMR ($CDCl_3$) 2.95 (s,3H), 3.09 (s,3H), 3.18 (s, 3H), 3.22 (s, 3H), 3.78 (3, 3H), 4.36 (d, J=3.0 Hz, 1H), 4.57 (dt, J=35.5, 3.0 Hz, 1H), 6.82 (d, J=8.0 Hz, 2H), 7.21 (d, J=8.0 Hz, 2H). ^{19}F NMR -97.01 (dd, J=285.7, 17.2 Hz, 1F), -98.22 (dd, J=285.7, 17.2 Hz, 1F). ^{13}C NMR 28.42, 37.07, 37.24, 50.62, 51.25 (t, J=24.1 Hz), 55.09, 113.86, 117.50 (t, J=262.3 Hz), 124.24, 130.97, 150.92, 159.68, 162.78 (t, J=28.6 Hz), 166.78, 167.13. HRMS (CI) Calcd for $C_{18}H_{22}F_2N_3O_5$: 398.1528. Found: 398.1513. Element Anal. For $C_{18}H_{21}F_2N_3O_5$: C, 54.41; H, 5.33; N, 10.57. Found: C, 54.04; H, 5.33; N, 10.42.

N,N-dimethyl-3-(1,3-dimethyl-2,4,6-trioxohexahydro-5-pyrimidiryl)-2,2-difluoro-3-(4-fluorophenyl) propanamide, **127c**

Yield: 86%; mp: 98-99°C; ^{1}H NMR 2.95 (s,3H), 3.14 (s, 3H), 3.18 (s, 3H), 4.32 (d, J=3.3 Hz), 4.68 (td, J=18.4, 3.3 Hz), 7.01 (t, J=8.5 Hz), 7.33 (dd, J=7.7, 5.2 Hz). ^{19}F NMR -96.69 (dd, J=285.6, 16.9Hz, 1F), -98.07 (dd, J=285.6, 16.9Hz, 1F), -133.25 (m, 1F). ^{13}C NMR 28.57, 28.64, 37.12 (t, J=8.1 Hz), 37.29, 50.76 (t, J=16.0 Hz), 115.57 (d, J=21.8 Hz), 117.41 (t, J=260.0 Hz), 128.87, 131.81 (d, J=6.9 Hz), 150.94, 162.77 (d, J=248.5 Hz), 126.32 (t, J=28.6 Hz), 166.67, 166.82. HRMS (EI) Calcd for $C_{17}H_{19}F_3N_3O_4$:

386.1327. Found: 386.1379. Element Anal. For $C_{17}H_{18}F_3N_3O_4$: C, 52.99; H, 4.71; N, 10.88. Found: C, 52.99; H, 4.82; N, 10.89.

N,N-dimethyl-3-(1,3-dimethyl-2,4,6-trioxohexahydro-5-pyrimidiryl)-2,2-difluoro-3-(4-bromophenyl) propanamide, **127d**

Yield: 82%; mp: 135-137°C; ^{1}H NMR ($CDCl_3$) 2.94 (s, 3H), 3.16 (s, 3H), 3,17 (s, 3H), 3.25 (s, 3H), 4.29 (d, J=3.6 Hz), 4.67 (td, J=18.4, 3.6 Hz), 7.24 (d, J=7.7Hz), 7.45 (d, J=7.7Hz). ^{19}F NMR-96.39 (dd, J=285.7, 17.1 Hz), -97.76 (dd, J=285.7, 17.1 Hz). ^{13}C NMR 28.60, 28.65, 37.07, 37.24, 50.58, 50.79 (t, J=22.9 Hz),117.29 (t, J=260.0 Hz), 122.95, 131.69, 132.30, 150.88, 162.21 (t, J=28.6 Hz), 166.55, 166,61. HRMS (CI) Calcd for $C_{17}H_{19}BrF_2N_3O_4$: 446.0527. Found: 446.0466. Element Anal. For $C_{17}H_{18}BrF_2N_3O_4$: C, 45.76; H, 4.07; N, 9.42. Found: C, 45.84; H, 4.00; N, 9.36.

3-(1,3-dimethyl-2,4,6-trioxohexahydro-5-pyrimidinyl)-2,2-difluoro-3-phenylpropanic acid, **128a**

Compound **127a** was dissolved in methylene chloride (20mL), and stirred at refluxing with 36% HCl (0.2 mL) for 2 hours. ^{19}F NMR showed that the reaction was finished. Methylene chloride (20 mL) was added and washed with water (2 x 10 mL), dried by $MgSO_4$. The solvent was removed to give a solid which was dissolved in saturated aqueous $NaHCO_3$ solution (30 mL) and washed with methylene chloride (2 x 10 mL). The aqueous solution was acidified (pH<ca. 3.0) with 6N HCl and was extracted with CH_2Cl_2 (3 x 10 mL). The extracts were washed with water ade dried ($MgSO_4$), and the solvent was removed to give a solid product.

Yield: 89%; mp: 116-118°C; ^{1}H NMR 3.08 (s, 3H), 3.21 (s, 3H), 4.15 (d, J=3.3 Hz, 1H), 4.36 (ddd, J=17.3, 14.9, 3.3, 1H), 6.37 (br., 1 H), 7.18-7.40 (m, 5H). ^{19}F NMR -102.78 (dd, J=266.1, 14.7 Hz), -105.32 (dd, J=266.1, 14.7 Hz). ^{13}C NMR 28.66, 28.76, 51.32, 53.53 (t, J=18.6Hz), 116.87(t, J=258.3 Hz), 129.69, 130.13, 130.87, 132.80, 152.48, 165.43 (t, J=25.0 Hz), 168.16, 169.06. HRMS (CI) Calcd for $C_{15}H_{15}F_2N_2O_5$: 341.0949. Found: 341.0977. Element Anal. For $C_{15}H_{14}F_2N_2O_5$: C, 52.95; H, 4.15; N, 8.23. Found: 50.26, H; 4.46, N; 7.78.

3-(1,3-dimethyl-2,4,6-trioxohexahydro-5-pyrimidinyl)-2,2-difluoro-3-(4-methoxyphenyl)propanic acid, **128b**

Yield: 81%; mp: 116-118°C; ^{1}H NMR 3.10 (s, 3H), 3.22 (s, 3H), 3.79 (s, 3H), 4.11 (d, J=3.3 hz), 4.33 (ddd, J=22.2, 12.6, 3.3 hz), 6.83 (d, J=8.5 Hz), 7.15 (d, J=8.5 Hz). ^{19}F NMR -102.61 (dd, J=263.8, 13.5 Hz), -106.43 (dd, J=263.8, 13.5 Hz). ^{13}C NMR 28.51, 28.60, 50.76, 52.06 (t, J=22.9 Hz), 55.52, 114.74, 11647, 123.84, 132.01, 151.90, 161.04, 164.27 (t, J=32.1 Hz), 167.14, 168.23. HRMS (CI) Calcd. for $C_{16}H_{17}N_2F_2O_6$: 371.1054. Found: 371.1040. Element Anal. For $C_{16}H_{16}F_2N_2O_6$: C, 51.90; H, 4.35; N, 7.56. Found: C, 49.50; H, 4.55; N, 7.18.

3-(1,3-dimethyl-2,4,6-trioxohexahydro-5-pyrimidinyl)-2,2-difluoro-3-(4-fluorophenyl)propanic acid, **128c**

Yield: 86%; mp: 102-104°C; ^{1}H NMR 3.21(s, 3H), 3.23 (s, 3H), 4.05 (d, J=3.3 Hz), 4.46 (ddd, J=25.2, 9.6, 3.3 Hz), 7.02 (t, J=8.4 Hz), 7.30(t, J=5.1 Hz). ^{19}F NMR -100.98 (dd, J=261.2, 7.3 Hz, 1F), -108.65 (dd, J=261.2, 7.3 Hz, 1F), -112.04 (m, 1F). ^{13}C NMR

28.67, 49.67, 51.29 (t, J=21.8 Hz), 115.80 (d, J=20.6 Hz), 115.08 (t, J=255.4 Hz), 127.04, 131.7 (d, J=8.0 Hz), 150.74, 163.05 (d, J=248.1 Hz), 162.33 (t, J=31.4 Hz), 166.01, 166.45. HRMS (CI) Calcd. for $C_{15}H_{13}F_3N_2O_5$: 359.0855. Found: 359.1765. Element Anal. For $C_{15}H_{13}F_3N_2O_5$+ H_2O: C, 47.87; H, 3.98; N, 7.45. Found: C, 48.05; H, 4.03; N, 7.45.

3-(1,3-dimethyl-2,4,6-trioxohexahydro-5-pyrimidinyl)-2,2-difluoro-3-(4-bromophenyl)propanic acid, **128d**

Yield: 80%; mp: 188-190°C; ^{1}H NMR ($CDCl_3$) 2.94 (s, 3H), 2.95 (s, 3H), 4.19 (dd, J=23.6,11.3 Hz, 1H), 7.03 (d, J=8.0 Hz), 7.30 (d, J=8.0 Hz). ^{19}F NMR -99.86 (dd, J=263.7, 9.8 Hz), -104.67 (dd, J=263.7, 9.8 Hz). ^{13}C NMR 28.85, 50.70, 52.40 (t, J=21.8 Hz), 116.52 (dd, J=264.6, 251.9 Hz), 124.17, 132.45, 132.76, 132.89, 152.48, 165.19, 168.02, 168.57. HRMS (CI) Calcd for $C_{15}H_{13}F_2N_2BrO_5$: 399.9870. Found: 399.9864. Elemt. Anal. Calcd for $C_{15}H_{13}BrF_2N_2O_5$: C, 42.98; H, 3.13; N, 6.68. Found: C, 42.94; H, 3.06; N, 6.64.

N,N-dimethyl-3-(1,3-dimethyl-2,4,6-trioxohexahydro-5-pyrimidinyl)-2,2-difluoro-3-phenylpropanamide, **129a**

Yield: 93%; ^{1}H NMR ($CDCl_3$) 2.21(s,3H), 2.87 (s, 3H), 3.23 (s, 3H), 3.29 (s, 3H), 5.42 (dd, J=29.1, 13.5 Hz), 7.24 (m, 3H), 7.55 (d, J=7.0 Hz). ^{19}F NMR -90.07 (dd, J=248.9, 14.7 Hz), -97.1 (dd, J=248.9, 14.7 Hz). ^{13}C NMR 27.76, 37.41, 38.33, 45. 12 (t, J=22.9 Hz), 83.56 (d, J=9.2 Hz),121.18 (dd, J=258.81, 254.3 Hz), 126.70, 128.10, 129.21, 137.10, 153.05, 164.16, 165.05 (t, J=28.6 Hz). IR 3436.4 (-OH), 1660.5 (C=O), 1574.1

(C=O). HRMS (CI) Calcd for $C_{17}H_{20}F_2N_3O_4$: 368.1422. Found: 368.1418. Element Anal. For $C_{17}H_{19}F_2N_3O_4$: C, 55.58; H, 5.21; N, 11.44. Found: C, 55.27; H, 5.08; N, 11.32.

6,6-difluoro-1,3-dimethyl-5-phenyl-1,3,4,5,6,7-hexahydro-2H-pyrano[2,3-d]pyrimidine-2,4,7-trione, **130a**

The mixture of the acid 6a and acetic anhydride (1mL) was heated at 100°C under dry nitrogen for 30 minutes and the excess anhydride was then evaporated in vacuo. The solid residue was shown to be the lactones.

Yield: 89%; ^{1}H NMR: 3.30 (s, 3H), 3.53 (s,3H), 4.75 (dd, J=15.7, 2.7 Hz), 7.13, 7.42 (m, 5H). ^{19}F NMR: -100.82 (dd, J=265.4, 15.7 Hz), -116.79 (dd, J=265.4, 3.4 Hz). ^{13}C NMR: 28.51, 29.76, 44.57 (t, J=24.1 Hz), 89.69 (d, J=6.9 Hz), 111.81 (dd, J=261.1, 246.2 Hz), 127.99, 128.77, 129.27, 129.36, 130.68, 150.15, 151.92, 154.38 (t, J= 35.5 Hz), 166.57. HRMS (CI) Calcd for $C_{15}H_{12}N_2F_2O_4$: 322.0765. Found: 322.0762.

6,6-difluoro-1,3-dimethyl-5-(4-methoxy-phenyl)-1,3,4,5,6,7-hexahydro-2H-pyrano[2,3-d]pyrimidine-2,4,7-trione, **130b**

Yield: 93%; ^{1}H NMR: 3.33 (s, 3H), 3.55 (s, 3H), 3.78 (s,3H), 4.70 (dd, J=15.1, 3.3 Hz), 6.87(d, J=8.52Hz), 7.09 (d, J=8.52 Hz). ^{19}F NMR: -101.16 (dd, J=264.2, 15.2 Hz), -117.24(dd, J=264.2, 3.4 Hz). ^{13}C NMR: 28.56, 29.79, 43.86 (t, J= 22.9 Hz), 55.28, 89.87, 11.18 (dd, J=261.2, 246.2 Hz), 114.83, 122.34, 129.21, 130.90,150.19, 151.77, 154.58 (t, J=32.1 Hz), 160.25. HRMS (CI) Calcd. for $C_{16}H_{14}N_2F_2O_5$: 352.0871. Found: 352.0853.

6,6-difluoro-1,3-dimethyl-5-(4-fluoro-phenyl)-1,3,4,5,6,7-hexahydro-2H-pyrano[2,3-d]pyrimidine-2,4,7-trione, **130c**

Yield: 90%; ^{1}H NMR: 3.32(s, 3H), 3.54 (s,3H), 4.76 (dd, J=15.4, 3.1 Hz, 1H), 7.05 (t, J=8.6 Hz, 2H), 7.16 (dd, J=8.6, 5.5 Hz, 2H). ^{19}F NMR: -101.19 (dd, J=266.1, 14.7 Hz, 1F), 112.72 (m, 1F), -116.92 (d, J=263.7 Hz). ^{13}C NMR: 28.46, 29.71, 43.87 (t, J=24.2 Hz), 89.32 (d, J=6.6 Hz), 110.98 (dd, J=260.4, 246.2 Hz), 116.40 (d, J=21.7 Hz), 129.86 (d, J=8.5 Hz), 126.54, 150.05, 151.90, 160.27, 154.29 (t, J=35.8 Hz), 163.08 (d, J=249.3 Hz). HRMS (EI) Calcd. for $C_{15}H_{11}O_4N_2F_3$: 340.0671. Found: 340.0673.

6,6-difluoro-1,3-dimethyl-5-(4-bromo-phenyl)-1,3,4,5,6,7-hexahydro-2H-pyrano[2,3-d]pyrimidine-2,4,7-trione, **130d**

Yield: 91%; ^{1}H NMR: 3.32 (s, 3H), 3.54 (s, 3H), 4.71 (dd, J=15.9, 3.0 Hz), 7.05 (d, J=8.1 Hz), 7.48(d, J=8.1 Hz). ^{19}F NMR: -100.95 (dd, J=266.5,15.7 Hz), -116.66 (dd, J=266.5, 15.7 Hz). ^{13}C NMR: 28.57, 29.83, 44.18 (t, J=24.0 Hz), 89.14, 110.80 (dd, J=261.1, 247.4 Hz), 123.64, 129.69, 131.47, 131.98, 132.59, 150.04, 151.98, 154.18, 160.25. HRMS (CI) Calcd. for $C_{15}H_{11}N_2BrF_2O_4$: 399.9870. Found: 399.9864.

CHAPTER 6
SYNTHETIC AND MECHANISTIC ASPECTS OF THE REACTION OF 1,1-BIS(DIMETHYLAMINO)-2,2-DIFLUOROETHENE WITH ETHYL PROPIOLATE

6.1 Introduction

Cycloaddition reactions of enamines with electron-deficient alkynes are well documented.[176] In general, reactions of propiolates with enamines involve initial [2+2] cycloaddition reactions to form cyclobutene derivatives, with these cycloadducts undergoing a subsequent electrocyclic ring opening, quite often spontaneously. As is the case in the example given below (Figure 6-1), such an electrocyclic reaction is often followed by a rapid 1,5-hydrogen shift to alleviate the strain of the originally formed *cis,trans*-diene.[177] In the case of alicyclic enamines, the net result is a ring enlarged product two carbon atoms larger than the original.[178] Such ring-enlargement processes have been successfully used in the synthesis of medium-sized heterocycles,[179] azulenes,[180] and natural products.[181] Similar two carbon ring expansions can be carried out using silyl enol ethers, with Lewis acid catalysis.[182] Ketene acetals, O,N-acetals, and N,N-aminals also undergo similar reactions with acetylenic esters.[183]

In the course of our comprehensive study of the chemistry of difluoroketene aminal **103**, we have observed its [2+2] and [2+4] cycloadditions with electron-deficient alkenes. In this chapter, its reaction with ethyl propiolate has been examined, along with the formation and chemistry of its ring-opened product.

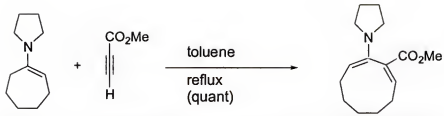
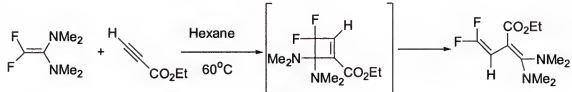


Figure 6-1. Cycloaddition reactions of enamines with electron-deficient alkynes.

6.2 Results and Discussion

The reaction of aminal **103** with ethyl propiolate was carried out in hexane at 60°C for 30 minutes to give diene **132** in 66% isolated yield (Figure 6-2). The formation of **132** occurs via a two step mechanism, the first being a [2+2] cycloaddition to form cyclobutene **131**. This step is then followed by a rapid ring-opening of **131** to form diene **132**.



103 **131** **132**

Figure 6-2. Cycloaddition of difluoroketene aminal with ethyl propiolate.

During the course of the reaction at 60°C, fluorine signals deriving from all three fluorinated species, **103** and **131-132**, were observed in the ^{19}F NMR spectrum of the reaction mixture. When the reaction was followed at room temperature by continuous monitoring of the ^{19}F NMR signals due to **103** (δ -113.45), **131** (δ -103.45) and **132** (δ

-96.71 and -92.91 ppm), the concentrations were seen to vary as shown in Figure 6-3. The observed growth and disappearance of cyclobutene **131** is consistent with the proposed reaction sequence above. Tracking the reaction at still lower temperatures, it was found that cyclobutene **131** is stable at temperatures below –15°C. Consequently, it was possible to measure the rate constant of the cycloaddition reaction at such low temperatures, and then to measure the rate constants of the isomerization of **131→132** at higher temperatures. Both the bimolecular rate constants of cycloaddition and the first-order rate constants of ring-opening were obtained using variable temperature NMR.

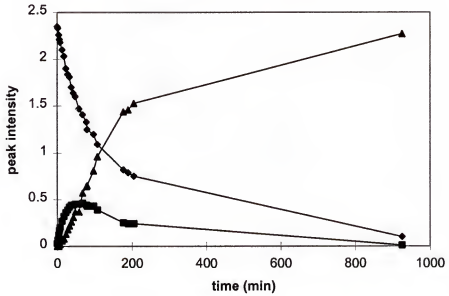
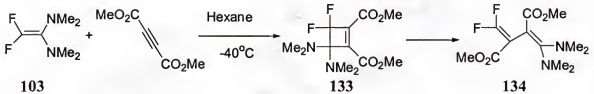


Figure 6-3. Concentration of **103**, **131** and **132** as a function of time in the reaction of **103** with ethyl propiolate in hexane at 20 °C; ◆: peak intensity of **103**; ■: peak intensity of **131**; ▲: peak intensity of **132**.

The reaction of **103** with dimethyl acetylene dicarboxylate was also carried out (Figure 6-4). At room temperature the reaction was complete in 10 minutes, but only an insoluble polymer product could be obtained. When the reaction was carried out at –40°C,

taking a ^{19}F NMR of the product mixture after 10 minutes indicated that a single product had been formed (singlet in the ^{19}F spectrum at δ -102.33 ppm). Cyclobutene **133** was proposed as the structure of this product, but when the solution containing **133** was allowed to warm to room temperature, no diene **134** was detected. Apparently, **134**, the respective ring-opening product of **133**, undergoes immediate polymerization when it is formed from **133** and attempts to isolate either **133** or **134** failed.



103 **133** **134**

Figure 6-4. Cycloaddition of difluoroketene aminal with dimethyl acetylene dicarboxylate.

6.2.1 The [2+2] Cycloaddition Reaction

The [2+2] cycloaddition reaction was initially studied at –35°C in $CDCl_3$: hexane (3:1), using an excess amount of ethyl propiolate (10 times to ketene aminal **103**) to ensure pseudo first order reaction conditions. A plot of the logarithm of the relative peak decrease, which is proportional to the consumption of the starting material (ketene aminal **103**), *versus* time, gave a straight line. The plot shown in Figure 6-5 indicated a pseudo first order process.

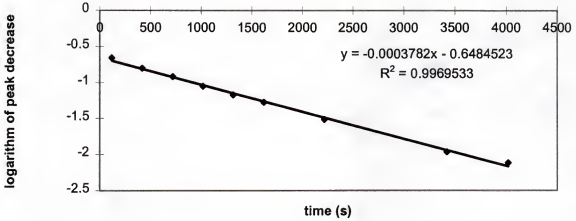


Figure 6-5. Determining the rate of [2+2] cycloaddition of **103** with ethyl propiolate at –35°C. The slope of the fitted line is $-3.78(0.25) \times 10^{-4}$, which is tantamount to a rate constant of $3.78(0.25) \times 10^{-4}\ S^{-1}$, R^2 is the square of regression.

Treated as a first order reaction, the observed rate constant, $\mathbf{k_{obs}}$, was obtained directly from the negative slope of the line (Equation 6-1), and the bimolecular rate constant was obtained by using Equation 6-2.

$$A \xrightarrow{k} B$$

$$rate = \frac{d[A]}{dt} = k[A]$$

$$\int \frac{d[A]}{[A]} = \int k dt$$

$$\ln\left(\frac{[A]_o}{[A]}\right) = kt$$

$$\ln[A]_t = -kt + \text{constant} \qquad \textbf{(6-1)}$$

$$k_{obs.} = k_{bimolec.}[M] \qquad \textbf{(6-2)}$$

Measurement of the bimolecular rate constants of [2+2] cycloaddition of **103** with ethyl propiolate, in $CDCl_3$: hexane (3:1) at five temperatures (-35 to –15°C), was carried out using variable temperature NMR, the obtained rate constants being given in Table 6-1.

Table 6-1. Rate constants for [2+2] cycloaddition reaction between **103** and ethyl propiolate in $CDCl_3$/hexane (3:1)

T(°C)	-35	-30	-25	-20	-15
$k/10^{-4}M^{-1}s^{-1}$	3.01±0.25	3.90±0.11	4.66±0.33	5.63±0.01	6.49±0.01

The enthalpy of activation, $\Delta H^{\neq}$, and entropy of activation, $\Delta S^{\neq}$, of the reaction were obtained from Eyring equations (Equation 6-3).

$$k = \left(\frac{kT}{h}\right)\exp\left(-\frac{\Delta H^{\neq}}{RT}\right)\exp\left(\frac{\Delta S^{\neq}}{R}\right) \qquad (6\text{-}3)$$

Where k is Boltzmann constant (1.38 x 10-23 JK^{-1}), h is Planck's constant (6.63 x 10^{-34} Js). The Eyring equation rearranges to Equation 6-4. A linear least square regression plot of ln(k/T) versus 1/T yielded $\Delta H^{\neq}$ and $\Delta S^{\neq}$ form the slope and the intercept respectively of the fitted line. The Eyring plot is shown in Figure 6-6.

$$\ln\left(\frac{k}{T}\right) = \ln\left(\frac{k}{h}\right) + \frac{\Delta S^{\neq}}{R} - \frac{\Delta H^{\neq}}{R}\frac{1}{T} \qquad (6\text{-}4)$$

$$\text{intercept} = \ln\left(\frac{k}{h}\right) + \frac{\Delta S^{\neq}}{R}, slope = -\frac{\Delta H^{\neq}}{R}$$

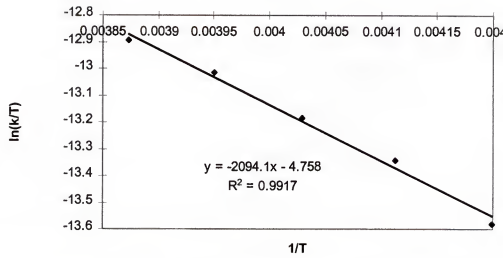


Figure 6-6. Eyring Plot of reaction. $\Delta H^{\neq}$=4.2 (0.4) kcal/mol; $\Delta S^{\neq}$=-56.7(0.9)eu

The activation parameters obtained for the cycloaddition process were: $\Delta H^{\neq} = 4.2$ ($\pm$0.4) kcal/mol and $\Delta S^{\neq} = -56.7(\pm 0.9)$ cal/K. This reaction is obviously largely entropy-controlled, and its huge observed negative activation entropy is reminiscent of those observed for ketene cycloadditions,[184] as well as those of [2+2] reactions proceeding via zwitterionic intermediates.[185] Mainly on the basis of product studies, concerted mechanisms have been proposed in some earlier reports of enamine-acetylenic ester cycloadditions.[186]

Rate constants were obtained in two different solvent mixtures at –20°C [3:1, $CDCl_3$/hexane and toluene-d_8/hexane], giving 5.63 ($\pm$ 0.01) x 10^{-4} and 1.2 ($\pm$0.03) x 10^{-4} $M^{-1}s^{-1}$, respectively, a k_{rel} of 4.7. A solvent effect of this magnitude, with the small range of solvent polarity, unfortunately doesn't provide any definitive mechanistic insight. The

kinetic results for this reactions are thus consistent with either the highly ordered transition state of a concerted reaction or a mechanism involving a zwitterion intermediate, the large $\Delta S^{\neq}$ of which would derive from severe solvent constriction.[184a, 185, 187]

6.2.2 Computational Study

In order to gain additional mechanistic insight into the [2+2] reaction between ketene aminal **103** and ethyl propiolate, the reaction was examined computationally (at MP26-31G*//RHF6-31G*, by Feng Tian).

A single transition state involving a concerted, but non-synchronous bond formation was able to be located. In the gas phase, the standard enthalpy of activation attaining this transition state ($\Delta H^{\neq}$) was calculated to be 13.6 kcal/mol, and the standard entropy of activation ($\Delta S^{\neq}$)was caculated to be –47.8 cal/mol.K. The reaction was found to be highly exothermic (ΔH^{o} = - 32.3 kcal/mol)

The structure of the transition state is depicted in Figure 6-7. In this transition state, the distance between C_{23} and C_2 where the C-C bond is forming, is 2.029 Å, and the distance between C_{24} and C_1 where the other C-C bond is forming, is 3.015 Å. Bond C_{23}-C_{24} is losing triple bond character, its bond length changing from 1.186 Å to 1.228 Å . Bond C_{26}-C_{24} is developing some double bond character, with its bond length changing from 1.441 Å to 1.389 Å (as compared to reactants).

An analysis of atomic charges revealed that a substantial amount of charge is transferred (total 0.406 e) from **103** to ethyl propiolate in the transition state. Partial

negative charges are developed mainly at C_{24} (-0.126 e) and C_{26} (-0.141 e). On the other side, partial positive charges are developed mainly at C_1 (+0.101 e) and N_4 (+0.164 e).

Figure 6-7. Structure of transition state (from two different views of points). Optimized at HF/3-21G(d) level of theory.

Although all of the computational data indicate that the reaction would be a concerted, non-synchronous process with partial zwitterionic character in the gas phase, these results do not rule out the realistic possibility that under actual conditions of reaction in solution the reaction might well involve formation of a discrete zwitterionic intermediate.

6.2.3 Electrocyclic Ring-Opening Reaction

The rate constants for the cyclobutene ring-opening of **131** were obtained at six temperatures (-5 to 25 °C) (Table 6-2) and the following activation parameters were obtained: $\Delta H^{\neq} = 18.5$ ($\pm$0.6) kcal/mol and $\Delta S^{\neq} = -9.7$ ($\pm$1.0) cal/mol.K. These activation parameters were consistent with the reaction proceeding via a normal, though obviously

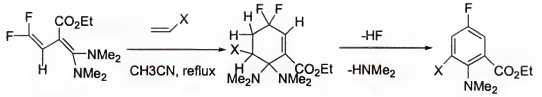
highly-activated electrocyclic ring-opening process. A much wider range of solvent conditions were able to be examined for this reaction, with the rate constants ranging from 3.16 ($\pm$0.07 x $10^{-4}M^{-1}s^{-1}$ for 3:1 acetonitrile/hexane to 1.37 ($\pm$0.17) x 10^{-4} $M^{-1}s^{-1}$ for 5:3 toluene-d_8/hexane, indicating little solvent effect for the reaction, a result consistent with the reaction's pericyclic nature.

Table 6-2. Rate Constants for Electrocyclic Ring Opening of Cyclobutene **131** in $CDCl_3$/Hexane (3:1)

T(°C)	-5	5	10	15	20	25
$K/10^{-4}s^{-1}$	0.41 ± 0.01	1.34 ± 0.04	2.41 ± 0.05	4.39 ± 0.09	8.25 ± 0.16	14.6 ± 0.2

6.2.4. Diels Alder Chemistry of Diene **132**

Recognizing that diene **132** might well play the role of reactive diene in Diels-Alder reactions, it was allowed to react with various electron-deficient dienophiles in refluxing acetonitrile. No primary adducts were obtained, Instead aromatic products, which were apparently formed via loss of HF and $HNMe_2$ from the presumed primary products, were isolated in fair to good yields (Figure 6-8). The proton and fluorine NMR spectra of the products indicate that **135a-d** are the probable structures. For example, **135a** exhibits two aromatic protons in the ^1H NMR at δ 7.28 and 7.39 ppm, each a doublets ($^3J_{HF}$ = 8.3 Hz, $^4J_{HH}$ = 3.1 Hz), and a triplet at δ -119.89 ppm in the $^{19}FNMR$ ($^3J_{HF}$ = 8.3 Hz), thus indicating that the two protons in **135a** are meta.



132 **135a-d**

135a, X = CN (41%); **b**, X = CO_2Me (40%); **c**, X= COMe (39%); **d**, X=CHO (26%)

Figure 6-8. Diels-Alder reactions of diene **132** with various electron-deficient dienophiles.

6.2.5 Conclusion

The unusually diverse reactive behavior of difluoro ketene aminal **103** was further demonstrated by the kinetic and computational study of its possibly concerted [2+2] reaction with ethyl propiolate. The resultant, thermally-unstable cyclobutene product, **131**, undergoes electrocyclic ring-opening below room temperature to produce diene **132**, which is observed to participate in Diels-Alder reactions with electron-deficient alkenes.

6.3 Experimental

1,1-Difluoro-4,4-bis(dimethylamino)-3-carboethoxy-1,3-butadiene, **132**. To a solution of 1,1-bis(dimethylamino)-2,2,2-trifluoroethane (1.7g, 10 mmol) in hexane (10 mL) at 0°C under nitrogen was added n-BuLi (2.5 M in hexanes, 4.5 mL), after which the reaction mixture was allowed to warm to room temperature and stirred 10 hours. Then the reaction mixture was distilled at reduced pressure into a 100 mL dry ice/acetone-cooled receiving flask equipped with rubber septum, magnetic stir bar, and a water cooled condenser. Before and after distillation, the total apparatus was maintained under a dry

nitrogen atmosphere. Ethyl propiolate (0.72g, 7.35 mmol) was added and the reaction mixture was stirred for 30 min. at 60 °C under dried nitrogen. The solvent was then distilled, and the residue removed under reduced pressure to give colorless liquid 1.2g (66%). bp 98-100 °C/0.9 mmHg. ^{1}H NMR δ 1.12 (t, J=7.1 Hz, 3 H), 2.60-3.10 (m, 12H), 4.17 (q, J=7.1 Hz, 2H), 5.45 (dd, J=27.8, 3.7 Hz, 1H). ^{19}F NMR δ -96.71 (d, J=48.4 Hz, 1F), -92.91 (dd, J=50.9, 26.6 Hz, 1F). ^{13}C NMR δ 15.20, 40.36 (m), 58.47, 72.28, 80.29 (dd, J=28.6, 16.0 Hz), 166.49, 154.47 (dd, 287.4, 279.4 Hz), 167.12. HRMS (EI) Calcd. for $C_{11}H_{18}F_2N_2O_2$: 248.1336, Found: 248.1313.

Ethyl 3-cyano-2-(dimethylamino)-5-fluorobenzoate, **135a**. In a 25 mL flask attached to a reflux condenser, compound 132 (0.34g, 1.37 mmol) was mixed with acrylonitrile (0.1g, in 5 mL of acetonitrile). The mixture was heated to reflux (became dark). And then stirred for 24 hours under reflux. 19F NMR spectra showed that the starting material 132 was gone. 10 mL of H_2O was added, the solution was extracted with diethyl ether (3 x 15 mL). All of the diethyl ether solutions were combined and washed with brine (2 x 10 mL), and dried with $MgSO_4$, and then the solvent was distilled. The residue was purified by column chromatography (hexane: ethyl acetate: 10:1) to give yellow product, 0.13g (41%). 1H NMR δ 1.33 (t, J=7.2 Hz, 3H), 2.88 (s, 6H), 4.32 (q, J=7.2 Hz, 2H), 7.28 (dd, J=7.3, 3.1 Hz, 1H), 7.39 (dd, J=8.1, 3.1 Hz,1H); 19F NMR δ -119.89 (t, J=7.3 Hz, 1F); 13C NMR δ 14.18, 43.52, 61.98, 111.10 (d, J=9.1 Hz), 116.98, 122.21 (d, J=23.7 Hz), 123.17 (d, J=24.5 Hz), 129.64 (d, J=6.5Hz), 152.01, 155.95 (d, J=245.8 Hz), 165.83; HRMS (CI) Cacld. for $C_{12}H_{14}FN_2O_2$ (M+1): 237.1039, Found: 237.1027.

N,N-Dimethyl 2-carbomethoxy-6-carboethoxy-4-fluoroaniline, **135b**. The procedure was the same as above except methyl acrylate was used as reagent. Yield: 30%. ^{1}H NMR δ 1.38 (t, J=7.5 Hz, 3H), 2.78 (s, 6H), 3.90 (s, 3H), 4.36 (q, J=7.5 Hz, 2H), 7.35 (d. J=8.2 Hz, 2H); ^{19}F NMR δ -120.32 (t, J=7.3 Hz, 1F); ^{13}C NMR δ 14.17, 43.49, 52.48, 61.49, 119.42 (d, J=4.6 Hz), 119.72 (d, J=4.6 Hz), 131.00, 131.74, 147.37, 156.80 (d, J=243.9 Hz), 166.92, 167.24; HRMS (EI) Calcd. for $C_{13}H_{16}FNO_4$: 269.1063, Found: 269.1023.

Ethyl 3-acetyl-2-(dimethylamino)-5-fluorobenzoate, **135c**. The procedure was the same as above except that methyl vinyl ketone was used as reagent. Yield: 39%. ^{1}H NMR δ 1.34 (t, J=7.14 Hz, 3H), 2.45 (s, 3H), 2.71 (s, 6H), 4.32 (q, J=7.14 Hz, 2H), 7.08 (dd, J=7.69, 3.02 Hz, 1H), 7.29 (dd, J=8.24, 3.02 Hz, 1H); ^{19}F NMR δ -118.83 (t, J=7.27 Hz, 1F); ^{13}C NMR δ 14.23, 29.44, 43.60, 61.75, 117.81 (d, J=22.9 Hz), 119.29 (d, J=24.1 Hz), 130.97, 142.11, 146.28, 157.79 (d, J=246.2 Hz), 166.93, 202.72; HRMS (M+1) Calcd. for $C_{13}H_{16}FNO_3$: 253.1114, Found: 253.1073.

Ethyl 2-(dimethylamino)-5-fluoro-3-formylbenzoate, **135d**. The procedure was the same as above except that acrolein was used as reagent. Yield: 26%. ^{1}H NMR δ 1.42 (t, J=7.2 Hz, 3H), 2.92 (s, 6H), 4.40 (q, J=7.2 Hz, 2H), 7.49 (dd, J=8.1, 3.2 Hz, 1H), 7.57 (dd, J=8.1, 3.2 Hz, 1H), 10.32 (d, J=3.1 Hz, 1H); ^{19}F NMR δ -118.17 (t, 7.27 Hz, 1F); ^{13}C NMR δ 14.21, 44.99, 61.92, 117.74 (d, J=22.7 Hz), 122.85 (d, J=24.7 Hz), 131.49 (d, J=6.6 Hz), 134.60 (d, J=6.1 Hz), 151.42, 157.96 (d, J=246.3 Hz), 166.65, 191.05; HRMS (EI) Cald. For $C_{12}H_{14}FNO_3$: 239.0958, Found: 239.0915.

Procedures for obtaining kinetic data

(a) Cycloaddition reaction of **103** with ethyl propioate

The kinetic experiments were run at five different temperatures in 3:1 of deuterated chloroform vs hexane: -15 , -20 , -25 , -30 and -35°C, and 3:1 of deuterated toluene vs hexane at -20°C. The peak intensity of difluoroketene aminal (starting material) was recorded relative to the peak intensity of internal standard α,α,α-trifluorotoluene. In these experiments an excess of ethyl propiolate [1.26M] was used to insure pseudo first order conditions.

0.2 mL of a solution of ketene aminal **103** was added in an NMR tube containing 0.6 mL of deuterated chloroform with around 7mg of α,α,α-trifluorotoluene as an internal standard. The NMR tube was cooled to -40°C and then 89.4mg of ethyl propiolate was added. The reaction progress was monitored by ^{19}F NMR using variable NMR kinetics.

A first order rate plot were made, plotting the logarithm of the relative peak decrease of **103** versus time. Straight lines were obtained indicating a probable pseudo-first order process and the observed rate constant, k_{obs}, was obtained. The bimolecular rate constants were obtained using $k_{obs.} = k_{bimolec.}$[ethyl propiolate]. ([ethyl propiolate] = 1.26M) and are given below.

The enthalpy of activation, $\Delta H^{\neq}$, and entropy of activation, $\Delta S^{\neq}$, of the reaction was obtained from the Eyring equation, $k = (kT/h) \exp(-\Delta H^{\neq}/RT)\exp(\Delta S^{\neq}/R)$, where k is Boltzmann constant (1.38×10^{-23} JK^{-1}), h is Planck's constant (6.63×10^{-34} Js). A linear

least squares regression plot of ln(k/T) versus 1/T yields $\Delta H^{\neq}$ and $\Delta S^{\neq}$ from the slope and the intercept.

Intercept = ln (k/h) + $\Delta S^{\neq}$, slope = - $\Delta H^{\neq}/R$. So $\Delta H^{\neq}$ = 2094.1 x 1.987 Cal/mol = 4.2 kcal/mol, $\Delta S^{\neq}/R$ = -4.758 - ln (k/h) =-4.758 - 23.65 = -28.52 K^{-1}, $\Delta S^{\neq}$ = -56.7 cal/mol K.

(b) Ring-opening Isomerization of Ethyl 4,4-bis(dimethylamino)-3,3-difluorocyclobutenecarboxylate, **131**.

The kinetic experiments were run at different solvents at 10 °C and run at six different temperatures in 3:1 of deuterated chloroform versus hexane. The peak intensity of **131** was recorded relative to the peak intensity of internal standard, α,α,α-trifluorotoluene.

First order rate plots of the data were made, plotting the logarithm of the relative peak decrease against time. Straight lines were obtained indicated a first order process and observede rate constant was obtained from the slope.

Tables of Kinetic Data

Cycloaddition reaction of **103** with ethyl propiolate

Table A-1. Data for determining the rate constant of cycloaddition at -35°C.

time (sec.)	120	420	720	1020	1320	1620	2220	3420	4020
ln(rel-peak intensity)	-0.654	-0.799	-0.916	-1.05	-1.171	-1.273	-1.514	-1.966	-2.12

Rate constant at -35 °C: k =3.01(±0.25) x 10^{-4} M^{-1} s^{-1}

Table A-2. Data for determining the rate constant of cycloaddition at -30 °C.

time (sec.)	120	420	720	1020	1320	1620	2220	2820	3420
ln(rel-peak intensity)	-0.868	-1.022	-1.171	-1.273	-1.427	-1.609	-1.897	-2.12	-2.526

Rate constant at -30 °C: k = 3.90 (0.11) x 10^{-4} M^{-1} s^{-1}

Table A-3. Data for determining the rate constant of cycloaddition at -25 °C.

time (sec.)	120	240	540	840	1140	1440	1740	2040
ln(rel-peak intensity)	-0.994	-1.079	-1.273	-1.386	-1.561	-1.772	-1.966	-2.12

Rate constant at -25 °C: $k = 4.66\ (0.03) \times 10^{-4}\ M^{-1}\ s^{-1}$

Table A-4. Data for determining the rate constant of cycloaddition at -20 °C.

time (sec.)	120	240	540	840	1140	1440	1740	2040
ln(rel-peak intensity)	-1.05	-1.139	-1.347	-1.561	-1.772	-1.966	-2.207	-2.408

Rate constant at -20 °C: $k = 5.63\ (0.01) \times 10^{-4}\ M^{-1}\ s^{-1}$

Table A-5. Data for determining the rate constant of cycloaddition at -15 °C.

time (sec.)	120	240	540	840	1140	1440	1740	2040
ln(rel-peak intensity)	-0.868	-0.968	-1.204	-1.47	-1.715	-1.966	-2.207	-2.408

Rate constant at -15 °C: $k = 6.490\ (0.001) \times 10^{-4}\ M^{-1}\ s^{-1}$

Table A-6. Arrhenium plot data for cycloaddition.

1/T	0.00420	0.00411	0.00403	0.00395	0.00387
ln(k)	-8.11	-7.85	-7.67	-7.48	-7.34

Table A-7. Eryring plot data for cycloaaditon.

1/T	0.0042	0.00411	0.00403	0.00395	0.00387
ln(k/T)	-13.58	-13.343	-13.186	-13.016	-12.894

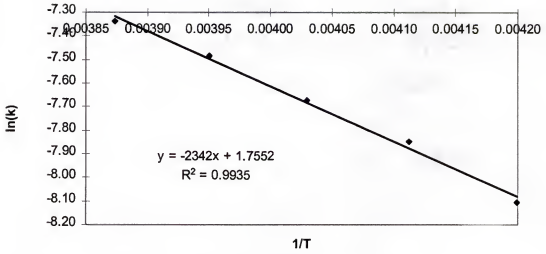


Figure A-1. Arrhenium plot for cycloaddition, Ea=4.7 (0.4) kcal/mol; logA = 0.8.

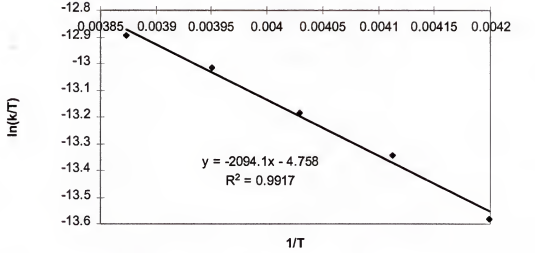


Figure A-2. Eryring plot for cycloaaditon, $\Delta H^{\neq}$=4.2 (0.4) kcal/mol; $\Delta S^{\neq}$=-56.7(0.9)eu.

Table A-8. Data for determining rate constant of cycloaddition of **103** with ethyl propiolate in 3:1 of deuterated toluene versus hexane at -20 °C

time (sec.)	120	240	540	840	1140	1440	1740
ln(rel-peak intensity)	-0.598	-0.616	-0.654	-0.693	-0.755	-0.799	-0.844
	2040	2340	2640	2940	3540	4140	4740
	-0.892	-0.942	-0.994	-1.05	-1.109	-1.204	-1.273

Rate constant at -20 °C in 3:1 toluene vs hexane: $k = 1.20\ (0.02) \times 10^{-4}\ M^{-1}\ s^{-1}$

(b) Ring-opening Isomerization of Ethyl 4,4-bis(dimethylamino)-3,3-difluorocyclobutenecarboxylate **131**

The kinetic experiments were run at different solvents at 10 °C and run at six different temperatures in 3:1 of deuterated chloroform *versus* hexane using α,α,α-trifluorotoluene as internal standard. The peak intensity **131** was recorded relative to the peak intensity of α,α,α-trifluorotoluene.

First order rate plots of the data were made, plotting the logarithm of the relative peak decrease against time. Straight lines were obtained indicated a first order process and observed rate constant was obtained from the slope.

Rate data for electrocyclic Ring-Opening of Cyclobutene **131**

Table B-1. Data for the rate determining for ring-opening in 5:3 of deuterated methylene chloride *versus* hexane at 10 °C.

time(sec.)		420	720	1020	1320	1620	1920
ln(rel-peak intensity		-0.416	-0.494	-0.545	-0.616	-0.713	-0.755

Rate constant in 5:3 of methylene chloride vs hexane:k=2.31(0.19) x $10^{-4}(s^{-1})$

Table B-2. Data for the rate determining for ring-opening in 5:3 of deuterated toluene *versus* hexane at 10 °C.

time (sec.)	120	420	720	1020	1320	1620	1920
ln(rel-peak intensity)	-0.968	-0.994	-1.05	-1.109	-1.139	-1.171	-1.204

Rate constant in 5:3 of toluene vs hexane: k=1.37 (0.17)x$10^{-4}(s^{-1})$

Table B-3. Data for the rate determining for ring-opening in 5:3 of deuterated chloroform *versus* hexane at 10 °C.

time(sec.)	120	420	720	1020	1320	1620	1920
ln(rel-peak intensity	-0.511	-0.562	-0.635	-0.693	-0.755	-0.821	-0.868

Rate constant in 5:3 of chloroform vs hexane: k=2.04(0.09)x$10^{-4}(s^{-1})$

Table B-4. Data for the rate determining for ring-opening in 3:1 of deuterated acetonitrile versus hexane at 10 °C.

time (sec)	300	600	900	1200	1500	1800	2400
ln(rel-peak intensity)	-0.916	-0.994	-1.079	-1.204	-1.309	-1.387	-1.56

Rate constant in 3:1 of acetonitrile vs hexane: $k=3.16(0.07)x10^{-4}(s^{-1})$

Table B-5. Data for the rate determining for ring-opening in 3:1 of deuterated chloroform *versus* hexane at 25 °C

time (sec.)	0	60	120	180	240	360	480	600	720
ln(rel-peak intensity)	-0.083	-0.163	-0.274	-0.371	-0.462	-0.635	-0.799	-0.968	-1.139

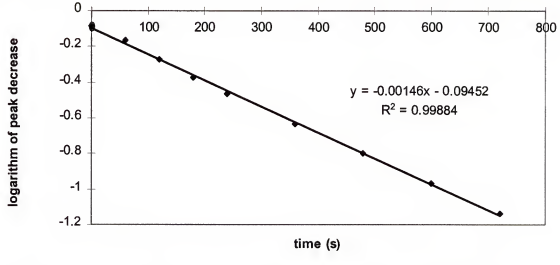


Figure B-1. Plot of data for the rate determining for ring-opening in 3:1 of deuterated chloroform *versus* hexane at 25 °C, $k = 1.46\ (0.02) \times 10^{-3}\ s^{-1}$.

Table B-6. Data for the rate determining for ring-opening in 3:1 of deuterated chloroform *versus* hexane at 20 °C.

time (s)	0	120	240	360	480	600	720	1020	1320
ln(rel-peak intensity)	-0.083	-0.151	-0.248	-0.357	-0.478	-0.58	-0.693	-0.916	-1.139

Rate constant at 20 °C: $k= 8.25\ (0.16) \times 10^{-4}\ s^{-1}$

Table B-7. Data for the rate determining for ring-opening in 3:1 of deuterated chloroform *versus* hexane at 15 °C.

time (sec.)	0	120	420	720	1020	1320	1620	1920
ln(rel-peak intensity)	-0.01	-0.041	-0.151	-0.274	-0.416	-0.562	-0.693	-0.844

Rate constant at 15 °C: $k = 4.39\ (0.09) \times 10^{-4}\ s^{-1}$

Table B-8. Data for the rate determining for ring-opening in 3:1 of deuterated chloroform *versus* hexane at 10 °C.

time (sec.)	0	120	420	720	1020	1320	1620	1920	2220	2520	2820
ln(rel-peak intensity)	0.03	-0.01	-0.062	-0.128	-0.198	-0.288	-0.371	-0.446	-0.528	-0.562	-0.635

Rate constant at 10 °C: $k = 2.41\ (0.05) \times 10^{-4}\ s^{-1}$

Table B-9. Data for the rate determining for ring-opening in 3:1 of deuterated chloroform *versus* hexane at 5 °C.

time (s)	0	120	420	720	1020	1320	1620	1920
ln(rel-peak intensity)	0.0676	0.0296	0	-0.0305	-0.0408	-0.0834	-0.117	-0.174
	2220	2520	2820	3120	3720	4220	4820	
	-0.211	-0.274	-0.315	-0.371	-0.431	-0.462	-0.598	

Rate constant at 5 °C: $k = 1.34\ (0.04) \times 10^{-4}\ s^{-1}$

Table B-10. Data for the rate determining for ring-opening in 3:1 of deuterated chloroform *versus* hexane at -5°C.

time (s)	0	420	1020	1620	2220	2820	3720	5020
ln(rel-peak intensity)	0.0198	0	-0.041	-0.062	-0.083	-0.117	-0.163	-0.198
	6220	6940	7540	8140	9040	9640	10240	
	-0.236	-0.274	-0.301	-0.329	-0.357	-0.386	-0.4	

Rate constant at -5 °C: $k = 4.05\ (0.06) \times 10^{-5}\ s^{-1}$

Table B-11. Arrheniums plot from data as showed above

1/T	0.00335	0.00341	0.00347	0.00353	0.0036	0.00373
ln(k)	-6.53	-7.10	-7.73	-8.33	-8.92	-10.11

Table B-12. Eyring plot data from the rate constants

1/T	0.00335	0.00341	0.00347	0.00353	0.0036	0.00373
ln(k/T)	-12.23	-12.78	-13.39	-13.98	-14.55	-15.71

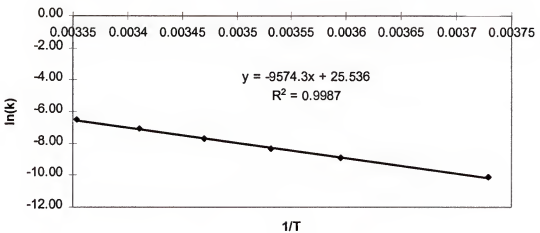


Figure B-2. Arrheniums plot for ring-opening, Ea= 19.0 (0.6) kcal/mol, logA=11.7(0.8)

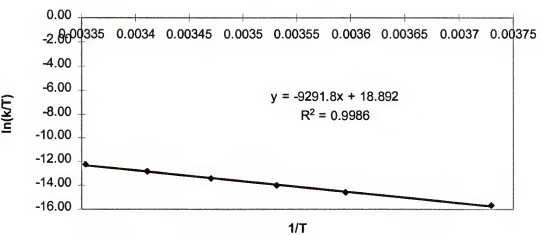


Figure B-3. Eyring plot for ring-opening, $\Delta H^{\neq}$=18.5 (0.6) kcal/mol; $\Delta S^{\neq}$=9.5(0.9)eu

Table B-13. Trace the cycloaddition reaction of difluoroketene aminal with ethyl propiolate at room temperature in hexane

time (sec.)	0	2	4	6	8	13	18	23	28	38	43	48	58
intensity(103)	2.35	2.33	2.26	2.21	2.18	2.1	2.03	1.9	1.84	1.7	1.64	1.6	1.47
intensity(131)	0.03	0.07	0.12	0.17	0.2	0.27	0.32	0.36	0.39	0.44	0.44	0.45	0.45
intensity(132)	0	0	0	0.02	0.02	0.06	0.08	0.13	0.18	0.26	0.31	0.37	0.46
time (sec.)	68	78	80	82	87	97	107	117	180	190	195	205	925
intensity(103)	1.41	1.33	1.25	1.29	1.28	1.2	1.09	0.82	0.81	0.79	0.77	0.75	0.1
intensity(131)	0.46	0.44	0.43	0.43	0.45	0.43	0.4	0.25	0.25	0.24	0.24	0.24	0.01
intensity(132)	0.57	0.64	0.65	0.68	0.75	0.81	0.87	1.44	1.44	1.47	1.46	1.53	2.27

Computational Methods

All the calculations were performed using the Gaussian 94W program package. Reactants, product and transition structure were optimized at restricted Hartree-Fock (HF) level of theory using the 3-21G(d) basis set. Frequency calculation was performed at the same level of theory to identify the saddle point and minima, and also to obtain zero point energies (scaled by 0.9409). Single point energies were computed at restricted Becke_style 3-Parameter (B3LYP) level of theory using the 6-31G(d) basis set. Atomic charge distribution was calculated using CHelpG scheme.

REFERENCES

1. Fried, J.; Sabo, E. F. *J. Am. Chem. Soc.* **1954**, 76, 1455.

2. (a) Hudlicky, M. *Chemistry of Organic Fluorine Compounds* Ellis Horwood, Chichester, **1976**. (b) Welch, J. T.; Eswarakrishnan, *Fluorine in Bioorganic Chemistry* Wiley, New York, **1991**. (c) Kukhar, V. P.; Soloshonok, V. A., Eds. *Fluorine-containing Amono Acids* Wiley, New York, **1995**. (d) Filler, R.; Kobayashi, Y.; Yagupolskii, L. M. Eds., *Organic Compounds in Medicinal Chemistry and Biomedicinal Applications*, Elsevier, Amsterdam, **1993**.

3. (a) Heidelberger, C.; Chaughuri, N. K. *Nature* **1957**, 179, 663. (b) Duschinsky, R. Pleven, E. *J. Am. Chem. Soc.* **1957**, 79, 4559.

4. Sheppard, W. A.; Sharts, C. M. *Organic Fluorine Chemistry* Benjamin, New York, **1969**.

5. Resnati, G. *Tetrahedron* **1993**, 49, 9385. And references therein.

6. (a) Baker, W. A.; Shulgin, A. T. *Nature* (London), **1965**, 206, 712. (b) Doddrell, S.; Wenkert, E.; Demarco, P. V. *J. Mol. Spec.* **1969**, 32, 162.

7. (a) Chenoweth, M. B.; McCarty, L. P. *Pharmacol. Rev.* **1963**, 15, 673. (b) Martin, J. E.; Kirk, K. L.; Klein, D. C. *Endocrinology* **1980**, 106, 398.

8. (a) Welch, J. T. *Tetrahedron* **1987**, 43, 3123. (b) Begue, J. P.; Bonnet-Delpon, D. *Tetrahedron* **1991**, 47, 3207. (c) Hudlicky, M. *Chemistry of Organic Fluorine Compounds* Ellis Horwood, Chichester, **1992**. (d) Hudlicky, M.; Pavlath, A. E., Eds., *Chemistry of Organic Fluorine Compounds II* American Chemical Society, Washington, D. C., **1995**.

9. Xu, Y. L; Dolbier, W. R., Jr., Rong, X. X. *J. Org. Chem.* **1997**, 62, 1576.

10. (a) Dennis, L. M.; Veeder, J. M.; Rochow, E. G. *J. Am. Chem. Soc.* 1931, 53, 3263. (b) Hutchinson, J.; Sandford, G. *Elemental Fluorine in Organic Chemistry*, In *Topics in current Chemistry*, 193. (c) Wilkison, J. A. *Chem. Rev.* **1992**, 92, 505.

11. Tius, M. *Tetrahedron* **1995**, 24, 6605.

12. (a) Finger, G. C. *Advances in Fluorine Chemistry 2* Butterworths, London, **1961**. (b) Leech, H. R. *Chem. Ind.* (London), **1960**, 242. (c) Yoneda, N. *Tetrahedron* **1991**, 47, 5329.

13. A review: Wang, C. –L. J. *Org. Reactions* **1984**, 34, 319.

14. A review: Hudlicky, M. *Org. Reactions* **1988**, 35, 513.

15. Reviews: (a) Lal, G. S.; Pez, G.; Syvret, R. G. *Chem. Rev.* **1996**, 96, 1809. (b) Strekowski, L.; Kiselyov, A. S. *Adv. In Heterocyclic Chemistry* **1995**, v. 62.

16. Chambers, R. D., Eds. *Organic Fluorine Chemistry – Techniques and Synthons*, *Topics in Current Chemistry*, 193, Springer Verlag, Berlin, **1997**.

17. (a) Zhuravlv, M. V.; Burmakov, A. I.; Bloshchitsa, F. A. *Zh. Org. Khim.* **1982**, 18, 1825. b) Zhuravlv, M. V.; Sass, V. P.; Sokolov, S. V. *Ibid.* **1983**, 19, 44. (c) Levy, M.; Steinberg, M. Szware, M. *J. Am. Chem. Soc.* **1954**, 76, 5976.

18. Kiselyov, A. S.; Strekowski, L. *Tetrahedron* **1996**, 25, 291.

19. Begue, J. P.; Mesureur, D. J. *J. Fluorine Chem.* **1988**, 39, 271.

20. Yaskioka, H.; Takayama, C.; Matsuo, N. J. *Synth. Org. Chem. Jpn.* **1984**, 42, 809.

21. (a) Uneyama, K.; Momota, M.; Hayashida, K.; Itoh, T. *J. Org. Chem.* **1990**, 55, 5364; (b) Uneyama, K.; Momota, M. *Tetrahedron Lett.* **1989**, 30, 2265.

22. Tanaka, K.; Susuki, T.; Maeno, S.; Mitsuhashi, K. *Bull. Chem. Soc. Jpn.* **1987**, 60, 4480.

23. Uneyama, K.; Morimoto, O.; Yamashita, F. *Tetrahedron Lett.* **1989**, 30, 4821.

24. (a) Uneyama, K.; Watanabe, H. *Tetrahedron Lett.* **1991**, 32, 1459. (b) Uneyama, K. *J. Fluorine Chem.* **1997**, 97, 11.

25. Ishikawa, J.; Sonoda, T.; Kobayashi, H. *Tetrahedron Lett.* **1989**, 30, 1641.

26. Kubota, T. Ojima, M.; Tanaka, T. *J. Chem. Soc. Chem. Comm.* **1991**, 433.

27. Lim, J. T.; Yamasaki, T. Kitazume, T. *J. Org. Chem.* **1987**, 52, 3211.

28. Gajewski, J. J.; Gee, K. R.; Jurayg, J. *J. Org. Chem.* **1990**, 55, 1813.

29. (a) Uneyama, K.; Momota, M.; Hayashida, K.; Itoh, T. *J. Org. Chem.* **1990**, 55, 5364; (b) Uneyama, K.; Momota, M. *Tetrahedron Lett.* **1989**, 30, 2265.

30. Kobayashi, Y.; Yamamoto, K.; Kumadaki, I. *Tetrahedron Lett.* **1979**, 20, 4071.

31. Yoneda, N.; Matsuoka, S.; Miyaura, N. *Bull. Chem. Soc. Jpn.* **1990**, 63, 2124.

32. Linderman, R. J.; Lonikar, M. S. *Tetrahedron Lett.* **1987**, 28, 5271.

33. Ojima, I.; Okabe, M.; Kato, K. *J. Am. Chem. Soc.* **1988**, 110, 150.

34. (a) Jiang, B.; Xu, Y. Y. *J. Org. Chem.* **1991**, 56, 7336. (b) Hu, C. M.; Hong, F.; Xu, Y. Y. *J. Fluorine Chem.* **1993**, 64,1. (c) Xu, Y. Y.; Jin, F. Q.; Huang, W. Y. *J. Org. Chem.* **1994**, 59, 2638.

35. Hundscheid, F. J. A.; Tandon, V. K.; Rou, P. H. F. M. *Tetrahedron Lett.* **1988**, 29, 227.

36. (a) Shimizu, I.; Ishii, H.; Tasaka, A. *Chem. Lett.* **1989**, 1127. (b) Begue, J. P.; Charpentier-Morize, M. Nee, G. *J. Chem. Soc. Chem. Comm.* **1989**, 83.

37. Taguchi, T.; Nanba, R.; Nakazawa, M. *Tetrahedron Lett.* **1988**, 29, 227.

38. (a) Kitazume, T.; Ohnogi, T. Miyauchi, H.; Yamaza, T. *J. Org. Chem.* **1989**, 54, 5630. (b) Ruppert, I.; Schlich, K.; Volbach, W. *Tetrahedron Lett.* **1984**, 25, 2195.

39. Ishikawa, N.; Koh, M. G.; Kitazume, T.; Choi, S. W. *J. Fluorine Chem.* **1984**, 24, 419.

40. Watanabe, S.; Sakai, Y.; Kitazume, T.; Yamazaki, T. *J. Fluorine Chem.* **1994**, 68, 59.

41. Molines, H.; Wakselman, C. *J. Fluorine Chem.* **1980**, 16, 97.

42. Yamazaki, T.; Takita, K.; Ishikawa, N. *J. Fluorine Chem.* **1985**, 30, 357.

43. For boron enolates, see: (a) Iseki, K.; Oishi, S.; Kobayashi, Y. *Chem. Pharm. Bull.* **1996**, 44, 2003; (b) Iseki, K.; Oishi, S.; Kobayashi, Y. *Tetrahedron* **1996**, 52, 71. (c) Makino, Y.; Iseki, K.; Fujii, K.; Oishi, S.; Hirano, T.; Kobayashi, Y. *Chem. Lett.* **1994**, 1135. For a lithium enolate, see: (d) Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E. *Tetrahedron Lett.* **1988**, 29, 4665.

44. (a) Mikami, K.; Yajima, T.; Matsukawa, S.; Terada, M.; Uchimaru, T.; Maruta, M. *Tetrahedron* **1996**, 52, 85.(b) Mikami, K.; Takasakai, T.; Matsukawa, S.; Maruta, M. *Synlett* **1995**, 1057.

45. Ando, A.; Kitamura, T.; Aono, S.; Sato, H.; Omote, M.; Koyama, M.; Takagi, T.; Miki, T.; Kumadaki, I. *Heterocycles* **1993**, 35, 1309.

46. (a) Mikami, K.; Yajima, T.; Terada, M.; Uchimaru, T. *Tetrahedron Lett.* **1993**, 34. 7591. (b) Mikami, K.; Yajima, T.;Siree, N.; Terada, M.; Suzuki, Y.; Kobayashi, I. *Synlett* **1996**, 837. (c) Leveque, L.; Blanc, M. L.; Pastor, R. *Tetrahedron, Lett.* **1997**, 38, 6001.

47. (a) Braid, M.; Isersone, H.; Lawlore, F. *J. Am. Chem. Soc.* **1954**, 76, 4027. (b) Henne, A.; Pelley, R.; Alm; R. *J. Am. Chem. Soc.* **1950**, 72, 3370. (c) Shechter, H.; Conrad, F. *J. Am. Chem. Soc.* **1950**, 72, 3371.

48. (a) Tanaka, K.; Suzuki, T.; Maeno, S.; Mitsuhashi, K. *J. Heterocyclic Chem.* **1986**, 23, 1535. (b) Hashidzume, A.; Kajiwara, A.; Harada, A.; Kamachi, M.; Kusunoki, M. *Bull. Chem. Soc. Jpn.* **1995**, 68, 2025.

49. Guanti, G.; Nanfi, L.; Narisano, E.; Scolastico, C.; Nosone, E. *Synthesis* **1985**, 609.

50. Young, J. A.; Schmidt-Collerus, J. J.; Krimmel, J. A. *J. Org. Chem.* **1971**, 36, 347.

51. Crank, G.; Harding, D. R. K.; Szinai, S. S. *J. Med. Chem.* **1970**, 13, 1212.

52. Ishii, A.; Higashiyama, K.; Mikami, K. *Chem. Lett.* **1998**, 119.

53. Maki, Y.; Kimoto, H.; Fujii, S.; Senga, M.; Cohen, L. A. *J. Fluorine Chem.* **1988**, 39, 47.

54. (a) Fujii, S.; Maki, Y.; Kimoto, H.; Cohen, L. A. *J. Fluorine Chem.* **1986**, 30, 415. (b) Fujii, S.; Maki, Y.; Kimoto, H.; Cohen, L. A. *J. Fluorine Chem.* **1986**, 31, 415. (c) Fujii, S.; Maki, Y.; Kimoto, H.; Cohen, L. A. *J. Fluorine Chem.* **1987**, 35, 581.

55. Guy, A.; Lobgeois, A.; Lemaire, M. *J. Fluorine Chem.* **1986**, 32, 361.

56. Kubota, T.; IiJima, M.; Tanaka, T. *Tetrahedron Lett.* **1992**, 33, 1351.

57. (a) Loh, Teck-Peng; Li, X. R. *Chem. Commun.* **1996**, 1929. (b) Loh, T. P.; Li, X. R.; *Tetrahedron* **1999**, 5611.

58. Sakumo, K.; Kuki, N.; Kuno, T.; Tagagi, T.; Koyama, M.; Ando, A.; Kumadaki, I. *J. Fluorine Chem.* **1999**, 93, 165.

59. Funabiki, K.; Nojiri, M.; Matsui, M.; Shibata, K. *Chem. Commun.* **1998**, 2051.

60. (a) Fuchigami, T.; Ichikawa, S.; Kandeel, Z.; Konno, A.; Nonaka, T. *Heterocycles* **1990**, 31, 415. (b) Fuchigami, T.; Nakagawa, Y.; Nonaka, T. *J. Org. Chem.* **1987**, 52, 5491. (c) Fuchigami, T.; Ichikawa, S. *J. Org. Chem.* **1994**, 59, 607.

61. (a) Fuchigami, T.; Nakagawa, Y.; Nonaka, T. *Tetrahedron Lett.* **1986**, 27, 3869. (b) Fuchigami, T,; Yamamoto, K.; Nakagawa, Y. *J. Org. Chem.* **1991**, 56, 137. (c)

Fuchigami, T.; Shimijo, M.; Konno, A.; Nakagawa, K. *J. Org. Chem.* **1990**, 55, 6074. (d) Fuchigami, T.; Yamamoto, K.; Yano, H. *J. Org. Chem.* **1992**, 57, 2946.

62. Tidwell, T. T. *Angew. Chem. Int. Ed. Engl.* **1984**, 23, 20.

63. Rover-Kevers, M.; Vertommen, L.; Huys, F.; Merenyl, R.; Janousek, Z.; Viehe, H. G. *Angew. Chem. Int. Ed. Engl.* **1981**, 20, 1023.

64. Ates, C.; Janousek, Z. Viehe, H. G. *Tetrahedron Lett.* **1993**, 34, 5714.

65. Laduron, F.; Ates, C.; Viehe, H. G. *Tetrahedron Lett.* **1996**, 37, 5515.

66. Uneyama, K.; Momota, M.; Hayashida, K.; Itoh, T. *J. Org. Chem.* **1990**, 55, 5364.

67. Bonnet-Delpon, D.; Cambillau, C.; Charpentier-Morize, M.; Jacquot, R.; Mesureur, D.; Ourevitch, M. *J. Org. Chem.* **1988**, 53, 754.

68. Begue, J. P.; Bonnet-Delpon, D. *Tetrahedron* **1991**, 47, 3207.

69. Filler, R.; Kobayashi, Y.; Yagupolski, L. M.; Eds. *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications* Elsevier, Amsterda, **1993**.

70. (a) Hertel, L. W.; Kroin, J. S.; Misner, J. M. *J. Org. Chem.* **1988**, 53, 2406. (b) Schirlin, D.; Van Dorsselar, V.; Weber, F.; Weill, C.; Altenburger, J. M.; Neises, B.; Flynn, G.; Remy, J. M.; Tarnus, C. *Bioorg. Med. Chem.* **1993**, 3, 3. (c) Berkowitz, D. B.; Sloss, D. G. *J. Org. Chem.* **1995**, 60, 7047 and references therein.

71. (a) Tozer, M. J.; Herpin, T. F. *Tetrahedron* **1996**, 52, 8619. (b) Uneyama, K. *J. Synth. Org. Jpn.* **1993**, 51, 232. (c) Percy, J. M. *Contemp. Org. Synth.* **1995**, 251.

72. (a) Kuroboshi, M.; Hiyama, T. *Synlett* **1991**, 969. (b) Banks, R. E. *U.S.Patent* 5086178, 1992. (c) Langlois, B. R. *Tetrahedron Lett.* **1991**, 32, 3691.

73. (a) Shi, G. Q,; Cai, W. L. *J. Org. Chem.* **1995**, 60, 6289. (b) Shi, G. Q,; Cai, W. L. *J. Chem. Soc., Chem. Commun.* **1995**, 1969. (c) Shi, G. Q,; Cai, W. L. *Synlett* **1996**, 371. (d) Osipov, S. N.; Golubev, A. S.; Sewald, N.; Michel, T.; Kolomiets. A. F.; Fokin, A. V.; Burger, K. *J. Org. Chem.* **1996**, 61, 7521.

74. Fried, J.; Hallinan, E. A. *Tetrahedron Lett.* **1984**, 25, 2301.

75. Ishihara, T.; Yamanaka, T.; Ando, T. *Chem. Lett.* **1984**, 1165.

76. Kuroboshi, M.; Ishihara, T. *Tetrahedron Lett.* **1987**, 28, 6481.

77. Kuroboshi, M.; Ishihara, T. *Bull. Chem. Soc. Jpn.* **1990**, 63, 428.

78. Lang, R. W.; Schaub, B. *Tetrahedron Lett.* **1988**, 29, 2943.

79. Shen, Y.; Qi, M. *J. Fluorine Chem.* **1994**, 67, 229.

80. Curran, T. T. *J. Org. Chem.* **1993**, 58, 6360.

81. Altenburger, J. M.; Schirlin, D. *Tetrahedron Lett.* **1991**, 32, 7255.

82. Shono, T.; Kise, N.; Oka, H. *Tetrahedron Lett.* **1991**, 32, 6567.

83. Yoshida, M.; Suzuki, D.; Iyoda, M. *Synthetic Comm.* **1996**, 26, 2523.

84. Kawasaki, T.; Kitazume, T. *J. Fluorine Chem.* **1998**, 88, 99.

85. Yamana, Y.; Ishihara, T.; Ando, T. *Tetrahedron Lett.* **1983**, 24. 507.

86. Kitagawa, O.; Taguchi, T.; Kobayashi, Y. *Tetrahedron Lett.* **1988**, 29, 1803.

87. Kitagawa, O.; Hashimoto, A.; Kobayashi, Y.; Taguchi, T. *Chem. Lett.* **1990**, 1307.

88. Whitten, J. P.; Barney, C. L.; Huber, E. W.; Bey, P.; McCarthy, J. R. *Tetrahedron Lett.* **1989**, 30, 3649.

89. Braun, M.; Vonderhagen, A.; Waldwuller, D. *Liebigs Ann.* **1995**, 1447.

90. Andres, J. M.; Martinez, M. A.; Pedrosa, R.; Perez-Encabo, A. *Synthesis* **1996**, 1070.

91. Iseki, K.; Kuroki, Y.; Asada, D.; Kobayashi, Y. *Tetrahedron Lett.* **1997**, 38, 1447.

92. (a) Jin, F.; Jiang, B.; Xu, Y. *Tetrahedron Lett.* **1992**, 22, 1221. (b) Jin, F.; Xu, Y.; Huang, W. *J. Chem. Soc., Chem. Commun.* **1994**, 2117. (c) Jin, F.; Xu, Y.; Huang, W. *J. Chem. Soc., Perkin Trans 1* **1993**, 795.

93. (a) Brigaud, T.; Doussot, P.; Portella, C. *J. Chem. Soc., Chem. Commun.* **1994**, 2117. (b) Lefebvre, O.; Brigaud, T.; Portella, C. *Tetrahedron* **1999**, 55, 7233. (c) Lefebvre, O.; Brigaud, T.; Portella, C. *Tetrahedron* **1998**, 54, 5939. (d) Fleming, I.; Roberts, R. S.; Smith, S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1215.

94. (a) Kodama, Y.; Yamane, H.; Okumura, M.; Shiro, M.; Taguchi, T. *Tetrahedron* **1995**, 51, 12217. (b) Kodama, Y.; Okumura, M.; Yanabu, N.; Taguchi, T. *Tetrahedron Lett.* **1996**, 37, 1061.

95. Howarth, J. A.; Owton, W. M.; Percy, J. M. *J. Chem. Soc., Chem. Commun.* **1995**, 757.

96. (a) Uneyama, K.; Mizutani, G. *Chem. Commun.* **1999**, 613. (b) Uneyama, K.; Maeda, K.; Kato, T.; Katagiri, T. *Tetrahedron Lett.* **1998**, 39, 3741. (c) Uneyama, K.; Mizutani, G.; Maeda, K.; Kato, T. *J. Org. Chem.* **1999**, 64, XXXX. (d) Amii, H.; Kobayashi, T.; Hatamoto, Y.; Uneyama, K. *Chem. Commun.* **1999**, 1323. (e) Uneyama, K.; Kato, T. *Tetrahedron Lett* **1998**, 39, 587.

97. Easdon, J. C. Ph. D. Thesis, University of Iowa, Iowa City, IA, 1987.

98. Weigel, J. A. *J. Org. Chem.* **1997**, 62, 6108.

99. Qiu, Z. M.; Burton, D. J. *J. Org. Chem.* **1995**, 60, 5570.

100. (a) Tsukamoto, T.; Kitazume, T. *J. Chem. Soc., Chem. Commun.* **1992**, 795. (b) Tsukamoto, T.; Kitazume, T. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1177.

101. (a) Tanaka, K.; Nakai, T.; Ishikawa, N. *Chem. Lett.* **1979**, 175. (b) Gimbert, Y.; Moradpour, A.; Dive, G.; Dehareng, D.; Lahlil, K. *J. Org. Chem.* **1993**, 58, 4685. (c) Purrington, S. T.; Sheu, M. H. *Tetrahedron Lett.* **1992**, 33, 3289. (d) Purrington, S. T.; Samaha, N. F. *J. Fluorine Chem.* **1989**, 43, 229. (e) Purrington, S. T.; Sheu, M. H. *J. Fluorine Chem.* **1993**, 65, 165. (f) Muzard, M.; Portella, C. *Synthesis* **1992**, 965. (g) Muzard, M.; Portella, C. *J. Org. Chem.* **1993**, 58, 29. (h) Portella, C.; Shermolovich, Y. *Tetrahedron Lett.* **1997**, 38, 4063. (I) Laduron, F.; Nyns, C.; Janousek, Z.; Viehe, H. G. *J. Prak. Chem.* **1997**, 339, 697.

102. (a) Blank, I.; Mager, J.; Bergmann, E. D. *J. Chem. Soc.* **1955**, 2190. (b) Bergmann, E. D.; Szinai, S. *J. Chem. Soc.* **1956**, 1521. (c) Bergmann, E. D.; Schwarcz, J. *J. Chem. Soc.* **1956**, 3278.

103. (a) Poulter, C. D.; Mash, E. A.; Argyle, J. C.; Muscio, O. J.; Rilling, H. C. *J. Am. Chem. Soc.* **1979**, 101, 6761. (b) Brandange, S.; Dahlmann, O.; March, L. *J. Am. Chem. Soc.* **1981**, 103, 4452.

104. (a) Molines, H.; Massoudi, M. H.; Cantacuzene, D.; Wakselman, C. *Synthesis* **1983**, 322. (b) Nakai, H.; Hamanaka, N.; Miyaki, H.; Hayashi, M. *Chem. Lett.* **1979**, 1499.

105. Welch, J. T.; Eswarakrishnan, *Fluorine Molecules, Structure, Reactivity, Synthesis and Application* Liebman, J. L.; Greenberg, A.; Dolbier, W. R., Jr., Ed.; VCH: New York, **1988**, 123.

106. Bekker, R. A.; Melikyan, G. G.; Daytkin, B. L.; Knanyants, I. L. *Zh. Org. Khim.* **1976**, 12, 1379.

107. Qian, C. -P.; Nakai, T. *Tetrahedron* Lett. **1988**, 29, 4119.

108. Qian, C. –P.; Nakia, T.; Dixon, D. A.; Smart, B. E. *J. Am. Chem. Soc.* **1990**, 112, 4602.

109. Bohme, H. *Angew. Chem.* **1956**, 68, 224.

110. Cook, A. G. *Enamines, Synthesis, Structure and Reactions*. Marcel Dekker, New York and London, **1969**.

111. Smith, P. A. S. *Open-chain Nitrogen Compounds* 1. Benjamin, New York-Amsterdam, **1965**, 291.

112.Duhamel, L. *Chemistry of Amino, Nitroso, and Nitro compounds and their Derivatives*, Part 2, Supplement F; Patai, S.; Eds. Wiley, New York, **1982**, 849.

113.Krimmel, J. A.; Schmidt-Collerus, J. J.; Young, J. A.; Bohner, G. E.; Gray, D. N. *J. Org. Chem.* **1971**, 36, 350.

114. For example: Umemoto, T. Goto, Y. *J. Fluorine Chem.* **1986**, 31, 231.

115.Bonnet-Delpon, D.; Cambilau, C.; Charpentier-Morize, M.; Jacquot, R.; Mesucur, D.; Overitch, M. *J. Org. Chem.* **1988**, 53, 754.

116. Nakai, T.; Tanaka, T.; Setoi, H.; Ishikawa, N. *Bull. Chem. Soc. Jpn.* **1977**, 50, 3069.

117. Aoyma, H. PCT Int. Appl. WO 94 12,454; Chem. Abstr. 1994, 121, 179088b.

118. McClinton, M. A.; McClinton, D. A. *Tetrahedron* **1992**, 48, 6555.

119. Kiehlmann, E.; Menon, B. C.; McGillivray, N. *Can. J. Chem.* **1973**, 51, 3177.

120.Norcross, B. E.; Klinedinst, P. E., Jr.; Westheimer, F. H. *J. Am. Chem. Soc.* **1962**, 84, 797.

121.Tramontini, M. *Synthesis* **1973**, 703.

122.Schreiber, J.; Maag, H.; Hashimoto, N.; Eschenmoser, A. *Angew. Chem.* **1971**, 83, 355.

123.Cooper, M. S.; Rairhurst, R. A.; Heaney, H.; Papageorgious, G. Wilkins, R. F. *Tetrahedron* **1989**, 45, 1155.

124. (a) DeSolms, S. J. *J. Org. Chem.* **1976**, 41, 2659. (b) Dunn, A. D.; Kinnear, K. I. *J. Heterocycl. Chem.* **1985**, 22, 311.

125.Heaney, H.; Papageorgiou, G.; Wilkins, R. F. *J. Chem. Soc., Chem. Commun.* **1988**, 1161.

126. Komissarov, V. N.; Ukhin, L. Yu. *Zh. Org. Khi.* **1987**, 23, 1326.

127. Klaver, W. J.; Moolenaar, M. J.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1988**, 44, 3805 and references therein.

128.Huang, Z. T.; Wang, M. X. *The Chemistry of Enamines*, Part 2, Rappoport, Z. Ed. Wiley, Chichester, **1994**, 1303.

129.Ott, E.; Dittus, G.; Weisenberger, H. *Chem. Ber.* **1943**, 76, 84.

130.McElrain, S. M.; Tate, B. E. *J. Am. Chem. Soc.* **1945**, 67, 202.

131.Gompper, R.; Topel, W. *Chem. Ber.* **1962**, 95, 2871.

132.Gomper, R.; Schaefer, H. *Chem. Ber.* **1967**, 100, 591.

133.Chen, B. M.; Huang, Z. T. *J. Struct. Chem.* **1984**, 3, 27.

134.Destro, R.; Cosentino. U.; Moro, G.; Ortoleva, E.; Pilati, T. *J. Mol. Struct.* **1989**, 212, 97.

135.Baum, K.; Bigelow, S. S.; Nauyen, N. V.; Archibald, T. G.; Gilardi, R.; George, C. *J. Org. Chem.* **1992**, 57, 235.

136.Fritsch, J. M.; Weingarton, H.; Wilson, J. D. *J. Am. Chem. Soc.* **1970**, 92, 4038.

137. Chambers, R. D. *Fluorine in Organic Chemistry* Wiley, New York, **1973**.

138.(a) Hobbs, C. F.; Weingarten, H. *J. Org. Chem.* **1974**, 39, 918. (b) Hobbs, C. F.; Weingarten, H. *J. Org. Chem.* **1968**, 33, 2385. (c) Hobbs, C. F.; Weingarten, H. *J. Am. Chem. Soc.* **1969**, 91, 780.

139.Gandhi, S. S.; Gibson, M. S. *Can. J. Chem.* **1987**, 65, 2717.

140.Boger, D. L.; Weinreb, S. N. *Hetero Diels-Alder Methodology in Organic Synthesis* Academic, San Diego, CA, **1987**.

141.Thuy, V. M. *Bull. Soc. Chim. France* **1970**, 4429.

142.Opitz, G. Holtmann, H. *Annalen* **1965**, 684, 79.

143.Ficini, J. Besseyre, J.; D'Angelo, J.; Barbara, C. C. R. *Acad. Sci. Ser. C* **1970**, 271, 468.

144.Padias, A. B.; Hedrick, S. T.; Hall, H. K., Jr. *J. Org. Chem.* **1983**, 48, 3787.

145.Amice, Ph.; Conia, J. M. *Tetrahedron Lett.* **1974**, 479.

146.Ficini, J.; Krief, A. *Tetrahedron Lett.* **1970**, 885.

147.Noeman, M. H.; Heathcock, C. H. *J. Org. Chem.* **1988**, 53, 3370.

148.Tacconi, G.; Leoni, M.; Righetti, P.; Desimoni, G.; Oberti, R.; Comin, F. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2687.

149.Bridge, C. F.; O'Hagen, D. *J. Fluorine Chem.* **1997**, 82, 21.

150.Burnier, J. S.; Jorgensen, W. L. *J. Org. Chem.* **1983**, 48, 3923.

151.Coutts, R. T.; Casy, A. F. *Pyridine and its Derivatives*, Supplement IV Abramovitch, R. A., Ed. Wiley, New York, **1975**. 445.

152.(a) Jones, G. *Comprehensive Heterocyclic Chemistry* Katrizky, A. R. et al., Eds. Pergamon Press, Oxford, **1984**, 2, 395. (b) Barluenga, J.; Ferrero, M.; Palacios, F. *Tetrahedron* **1997**, 53, 4521.

153.(a) Mukaiyama, T. *Agnew. Chem. Int. Ed. Engl.* **1979**, 18, 707. (b) Comins, D. L.; Saha, J. K. *Tetrahedron Lett.* **1995**, 36, 7995.

154. Boudakian, M. M. in *Encyclopedia of Chemical Technology* Grayson, M. and Eckroth, K. O., Eds. 10, Wiley, New York, **1980**.

155.Boudakian, M. M. *J. Fluorine Chem.* **1981**, 18, 497.

156.Hand, E. S.; Baker, D. C. *Synthesis* **1989**, 905.

157.Stavber, S.; Zupan, M. *Tetrahedron Lett.* **1990**, 31, 775.

158.Meyers, A. I.; Sircar, J. C. *The Chemistry of the Cyano Group* Patai, S., Ed. Interscience, New York, **1970**, 341.

159. (a) Huisgen, R. *Angew. Chem.* **1963**, 75, 604. (b) Huisgen, R. *J. Org. Chem.* **1976**, 41, 403. (c) Tufariello, J. J. in *1,3-dipolar Cycloaddition Chemistry* Padwa, A. Ed. Wiley, New York, **1984**.

160.Torssell, K. B. *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*; VCH: New York, **1988**.

161. (a) Nomura, Y.; Furasaki, F.; Takeuchi, Y. *Bull. Chem. Soc. Jpn.* **1967**, 40, 1740. (b) Tsuge, O.; Tashiro, M.; Nishihara, Y. *Tetrahedron Lett.* **1967**, 3769. (c) Freeman, J. P.; Haddadin, M. J.; Hansen, J. F. *J. Org. Chem.* **1979**, 44, 4978. (d) Suschitzky, H.; Wakefield, B. J.; Whitten, J. P. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2709.

162.Nomura, Y.; Furusaki, F.; Takeuchi, Y. *Bull. Chem. Soc. Jpn.* **1970**, 43, 3002.

163.Kamm, O. *Organic Synthesis* I. Wiley, **1932**, 445.

164.Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, 110, 1238.

165.Fischer, E.; Von Mering, J. R. *Ther. Ggw.* **1903**, 44, 97.

166.Burger, A. *Medicinal Chemistry*, 3rd. ed. Wiley-Interscience, New York, **1970**, 1367.

167.Naguib, F. N. M.; Levesque, D. L.; Wang, Eng-Chi; Panzica, P. P.; El Kouni, M. H. *Biochem. Pharmaco.* **1993**, 46, 1273.

168.Levesque, D. L.; Wang, Eng-Chi, Wei, Dau-Chang; El Kouni, M. H.; Naguib, F. N. M. *J. Heterocyclic Chem.* **1993**, 30, 1399.

169.Resnati, G. *Farmaco* **1990**, 45, 1043.

170.Resnati, G. *Farmaco* **1990**, 45, 1137.

171.Bednar, R.; Haslinger, F.; Herzig, W.; Polansky, P.; Wolcshann, R. *Monatsch. Chem.* **1976**, 107, 1115.

172.De Meester, P.; Jovanovic, M. V.; Chu, S. S. C.; Biehl, E. R. *J. Heterocyclic Chem.* **1986**, 23, 337.

173.Wipfler, H.; Ziegler, E.; Wolfbeis, O. S.; Schauenstein, E. Z. *Naturforsch.* **1978**, 33b, 1016.

174.Tsolomitis, A.; Sandris, C. *J. Heterocyclic Chem.* **1983**, 20, 1545.

175.Battiste, M. A.; Strekowski, L.; Paryzek, Z. *Org. Proc. Res. & Develop.* **1997**, 1, 222.

176.Cook, A. G. Cycloaddition reaction of enamines, in *Enamines: Synthesis, Structure, and reactions*; Cook, G., Ed. Basel, New York, **1987**.

177. Vos, G. J. M.; Benders, P. H.; Reinhoudt, D. N.; Egberink, R. J. M.; Harkema, S.; van Hummei, G. J. *J. Org. Chem.* **1986**, 51, 2004.

178.Hesse, M. *Ring Enlargement in Organic Chemistry* VCH, Weinheim, **1991**.

179. Acheson, R. M.; Elmore, N. F. *Adv. Heterocycl. Chem.* **1978**, 23, 263.

180.Hafner, K.; Klâs, H. C.; Bõhm, M. C. *Tetrahedron Lett.* **1980**, 21, 41.

181. (a) Stock, G.; MacDonald, T. L. *J. Am. Chem. Soc.* **1975**, 97, 1264. (b) Becker, D.; Hughes, L. R.; Raphael, R. A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1674.

182.Clark, R. D.; Untch, K. G. *J. Org. Chem.* **1979**, 44, 248.

183.Brannock, K. C.; Burpitt, R. D.; Thwart, J. G. *J. Org. Chem.* **1962**, 28, 1697.

184.(a) Huisgen, R.; Feiler, L. A.; Otto, P. *Chem. Ber.* **1969**, 102, 3444. (b) Brady, W. T.; O'Neal, H. R. *J. Org. Chem.* **1967**, 32, 612.

185.Huisgen, R. *Acc. Chem. Res.* **1977**, 10, 117.

186.Reinhoudt, D. N.; Verboom, W.; Visser, G. W.; Trompenaars, W. O.; Harkema, S.; Hummel, G. J. *J.Am. Chem. Soc.* **1984**, 106, 1341.

187.Huisgen, R.; Otto, P. *J. Am. Chem. Soc.* **1968**, 88, 5342.

BIOGRAPHICAL SKETCH

Yuelian Xu was born in April 1966, in Shanghai, P. R. China. He received the B.S. degree in chemistry from Shanghai Tongji University in July 1989, and the M.S. degree in polymer science from Shanghai Jiaotong University in February 1992. From March 1992, to November 1994, he worked at Shanghai Organic Chemistry Institute, Academy of Sciences, as an assistant researcher. From December 1994 to December 1996, he worked with Professor William R. Dolbier, Jr., as a visiting scholar in the chemistry department of the University of Florida.

He started the Ph.D. program in the chemistry department of the University of Florida in January 1997, under the supervision of Professor Dolbier.

He is married to Hua Lou, who is now a graduate student in the research group of Dr. Weihong Tan. They have a five-year-old daughter, Qingyu Xu, who was born in Shanghai.

I certify that I have read this study and that in my opinion in confirms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

William R. Dolbier, Jr., Chair
Professor of Chemistry

I certify that I have read this study and that in my opinion in confirms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Merle A. Battiste
Professor of Chemistry

I certify that I have read this study and that in my opinion in confirms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Kirk S. Schanze
Professor of Chemistry

I certify that I have read this study and that in my opinion in confirms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Hai-Ping Cheng
Associate Professor of Physics

I certify that I have read this study and that in my opinion in confirms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Gus J. Palenik
Professor of Chemistry

This dissertation was submitted to the Graduate Faculty of the Department of Chemistry in the College of Liberal Arts and Sciences and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

December 1999

_____

Dean, Graduate School